A STUDY OF SOME ABNORMALITIES OF THE MONOSYNAPTIC REFLEX ARC IN MAN

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by

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CONTENTS

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INTRODUCTION:

Since it was brought to the attention of scientists by Erb (1875) and Westphal (1875), the tendon jerk has played a crucial part in the development of knowledge about the nervous system.

The course of this development can be divided into three main phases. The first was dominated by the controversy over the nature of the phenomenon (Liddell, 1960), and ended with the demonstration by Sherrington that it was a reflex contraction of a muscle evoked by stretching the muscle concerned.

The second phase saw the elaboration of this idea by the Sherrington school and the extension of knowledge about the behaviour of the stretch receptors. The third phase started with Leksell's (1945) discovery of the motor innervation of muscle spindles. It is characterised by the frequent borrowing of terms and ideas from the world of engineering.

The controversy over the nature of the jerk started in 1875. It is reflected in the different terms used to describe it. Erb (1875) called it a "tendon-reflex" but Westphal (1875) who believed that it was not a reflex but an intrinsic contraction of the muscle, preferred to call it the "tendon phenomenon". During the first attempts at recording the jerk by Burkhardt (1877), Waller (1880) and Brissaud (1880), its brief latency was noted and this was invoked as an argument by the'anti-reflexists'.

Clinical neurologists played an important part in the early stages of this controversy and, on the whole, appear to have favoured the reflex theory, possibly because of their clinical experience of patients with absent jerks. Gowers (1881a), for example, with characteristic foresight, applied the term "myotatic" to the jerk.

Although the brief latency was the main argument used against the suggested reflex nature of the jerk, the chief obstacle to its acceptance as such was probably the teleological attitudes that still prevailed at the time. There was, as Pieron (1921) has pointed out, a failure to realise the biological significance of the phenomenon. Reflexes were thought of as mechanisms adapted to definite aims and the only function of the tendon jerk seemed to be that of providing a useful clinical sign.

Sherrington closed the controversy by a series of crucial experiments which demonstrated reflex contraction of an extensor muscle in response to stretch and established the functional significance of the stretch reflex and its importance in postural adaptation.

During the second phase, our knowledge of the reflex pathway itself was greatly extended. Adrian and Zottermann (1926) and Matthews (1931 - 1933) studied the behaviour of the spindle afferents. Eccles and Pritchard (1937) and Renshaw (1940) prepared the ground for the demonstration by Lloyd (1943 a, b and c) of the monosynaptic connection between the large afferent fibres of a nerve root and the motorneurones of the same spinal segment. This received final histological confirmation from the work of Szentagothai (1948).

Definite histological confirmation of the origin of these large afferents from the annulospiral endings in muscle was obtained by Barker (1948) and this was reinforced by the electrophysiological evidence of Hunt (1954).

Until 1945 the stretch reflex appeared to be a comparatively simple mechanism which reacted in a very restricted way. When Leksell (1945) showed that muscle spindles were provided with motor innervation which could vary their sensitivity, the reflex appeared in a completely new light. It was seen as an extremely plastic mechanism with enormous possibilities of control. The possibilities were explored by Granit and his school and by Merton (1953) who introduced the idea of a "servo system" into this branch of physiology.

I have pointed out how, in the early stages of this development, clinical neurologists participated actively in the debate that was raging at the time and how they helped to establish the reflex nature of the tendon jerk. However, as anaesthetic and operative techniques improved and experimenters were led away from work on intact animals and on man, neurologists began to show reticence in accepting the results obtained by neurophysiologists as having any but the remotest relevance to the study of diseases of the nervous system. A few workers, notably Hoffmann (1918 - 1952) showd that useful results could be obtained by applying electrophysiological techniques to human subjects, but their work was largely ignored.

Later, Magladery et al (1950 a) confirmed Hoffmann's results showing that it was possible to stimulate the afferent fibres in the medial popliteal nerve and to produce a reflex contraction of the calf muscles, that is, a sort of ankle jerk which by-passes the muscle stretch receptors. Paillard (1955 a, 1955 b) used this technique to show that many of Sherrington's ideas applied to the human subject.

SCOPE:

Although there has been a tendency in clinical neurology to interpret spasticity and rigidity in terms of the discoveries of the Granit school (Hassler 1955 and 1956; Schaltenbrand 1956, Rushworth 1960) this has not been true of the study of the areflexias.

Absence of tendon jerks is still thought of entirely in terms of lesions in the peripheral nerves or nerve roots. There are a number of conditions in which the absence of reflexes is either left unexplained or given a totally unconvincing explanation.

These conditions include Friedreich's ataxia and allied diseases, cerebellar diseases, Holmes-Adie syndrome, some cases of Parkinsonism, epilepsy where there is often a loss of tendon jerks for a varying period after a fit, some cases of disseminated sclerosis with signs pointing to a lesion in the brain stem only, phenytoin intoxication and polymyositis. The effect of intrathecal phenol on the reflex arc has been ascribed (Iggo and Walshe 1960) to an effect on the gamma-efferent fibres but the evidence has been based almost entirely on animal experiments.

The present work is an attempt to apply current neurophysiological ideas to the study of these states. Occasionally it was possible to obtain confirmation by means of human experiments to what was already conjectured on the basis of animal experiments.

During this work it was found necessary to examine some of the indirect methods which have been claimed to be of value in deriving information about the behaviour of the motor nerves of muscle spindles in man. The possibilities and limitations of these methods are discussed very briefly.

This thesis will limit itself to the consideration of cases where the areflexia constitutes a problem and will not deal with conditions such as tabes dorsalis and the polyneuritides where the loss of tendon jerks is readily explicable by the lesions in the posterior nerve roots or peripheral nerves. These cases will only be mentioned in so far as they form a contrast to the others.

The clinical material was restricted to the cases available in the wards of the unit where this work was done. Some suitable cases were traced from out-patient records but on the whole this was not found to be a very useful source. The patients with cerebellar tumours and reflex abnormalities were obtained from a neurosurgical unit.

DIFFICULTIES:

The disadvantages of working on human subjects need hardly be stressed. Major difficulties arose from the fact that most of the subjects used were patients who had been admitted to hospital for investigation and treatment. Often the therapeutic programme would clash with the planning of an experiment and, naturally, the length and timing of the experiment would have to be adapted to suit such a programme.

Similarly, experiments had to be arranged so as to fit in with the hospital routine. Meals, visiting hours had to be kept in mind. Most of the patients were also used for undergraduate and post-graduate demonstrations and this also cut down the time for which they were available.

All these and other minor frustrations are not readily appreciated by animal experimenters and add considerably to the amount of time spent in order to complete any one experiment.

There are, of course, some major advantages in using human subjects. Not the least of these, is the possibility of having their complete co-operation without the need to resort to anaesthesia.

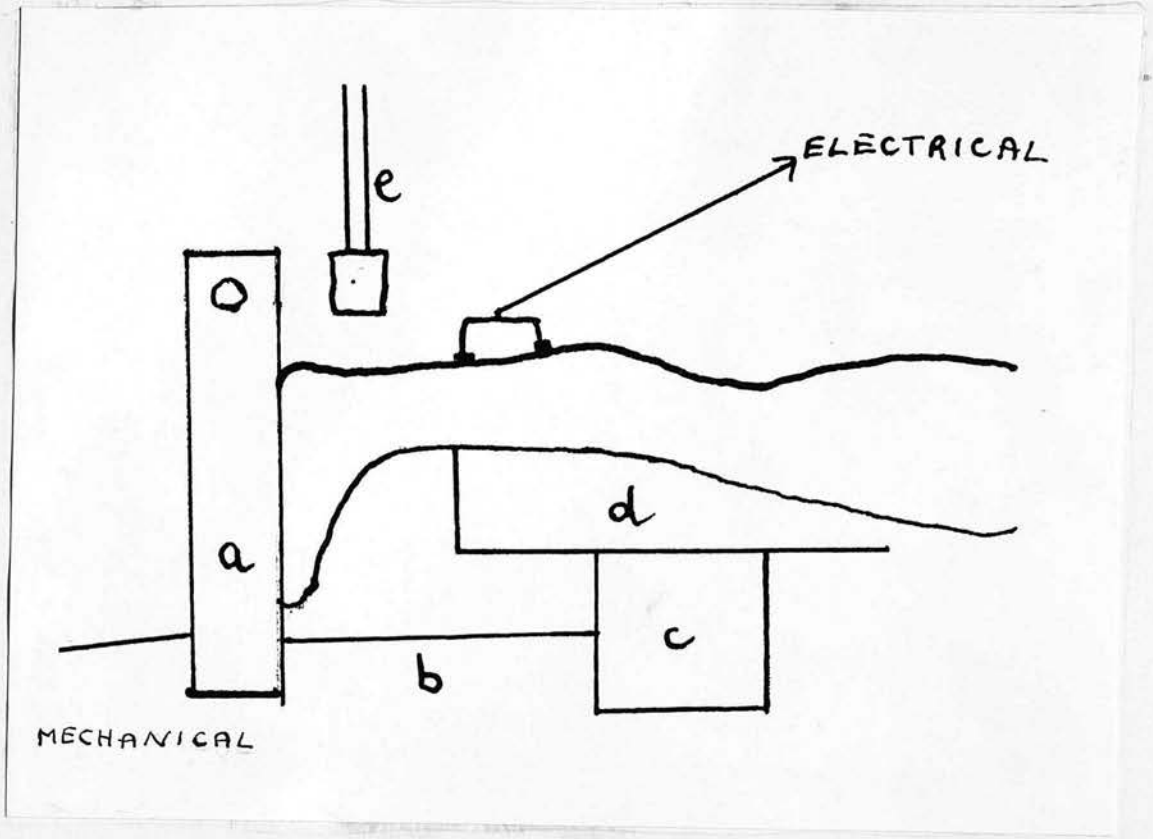


Fig. 1.

Fig. 1 - Arrangement for recording of the ankle jerk.

a) Hinged board

b) Rubber-coated wire

c) Transducer

d) Couch

e) Hammer

The methods used frequently throughout this investigation will be outlined here. Where additional methods were used in any special case, these will be described under the appropriate section.

METHODS:

Early on in this study it was decided that the ankle jerk would be the most convenient tendon reflex to use. This was partly because it is the easiest one to record and partly because all the work on electrically induced reflex contraction of muscles in man has been carried out on the medial popliteal nerve and the calf muscles.

It also happens that this tendon reflex is the one most commonly interfered with by diseases of the nervous system. The number of cases available was therefore reasonably large.

The position of the subject:

The subject lay prone on a couch with his feet hanging over the edge resting against a hinged board which was connected to the mechano-electric transducer (described later). The arrangement is shown in figure 1

Care was taken to see that the subject was comfortable and absolutely relaxed. Occasionally a subject was found to have fallen asleep in spite of the often unpleasant electrical stimulation that he was undergoing. This was probably due to the fact that the stimulation was regular. Oswald (1960) has shown that this is liable to induce sleep even if it is painful.

It was found to be important to guard against this and also to allow the patient to get used to the stimulation before the actual experiment was started, since Paillard (1955 a) has shown that sleep and emotional disturbances can affect the excitability of the motorneurones in the spinal cord and thus produce changes in the reflex arc. However, it was not found necessary to use irregular stimulation or to monitor the E.E.G. simultaneously like Paillard (1955 a). Consistent results could be obtained provided the subject was spoken to frequently to ensure that he was awake.

The tendon-hammer:

Many devices have already been suggested for the quantitative study of the tendon jerk. Most of them have been devised for eliciting the knee jerk (Castex 1902; Piéron 1910; Lee and Kleitmann 1923; Tuttle 1924; Johnson 1927). They can be broadly divided into 1) those where a hinged tendon hammer swings from a constant height or a free weight falls through a constant distance (Piéron 1910; Tuttle 1924)

2) those in which the system is operated by the sudden release of a spring (Lee and Kleitmann 1923) and

3) those employing the principle of the solenoid (Johnson 1927; Buller and Dornhorst 1957).

The solenoid-driven hammer is undoubtedly the neatest of these. However, it may, if it is used fairly near the electromyographic recording electrodes, produce troublesome electromagnetic interference (Nogués and Paillard 1953).

Nogués and Paillard (1953) have devised an admirable device with useful properties. It can elicit simultaneous or successive tendon jerks from two different sites. It allows a wide range of frequency of repetitive stimulation and can be used to trigger an oscilloscope trace or a stimulator at varying delay intervals.

Since my aims in this field were limited to eliciting single ankle jerks and since I was not concerned with timing, I used a very simple device (figure 2).

This consisted of a weight attached to the end of a stiff metal rod about two feet long and held above the tendo-Achilles by means of stiff elastic bands fixed on to a horizontal frame. The metal rod fitted into a shorter tube of slightly larger diameter which was also fixed to the frame. This was used to guide the weight on to the tendon. The rod was lifted through the tube to a constant height and suddenly released. The height of the frame and the length and elasticity of the rubber bands was chosen so as to allow the weight to hit the tendon only once.

Since all that was required was a method of delivering a blow that would remain constant for only a short time, any changes in the physical constants of the rubber bands could be ignored.

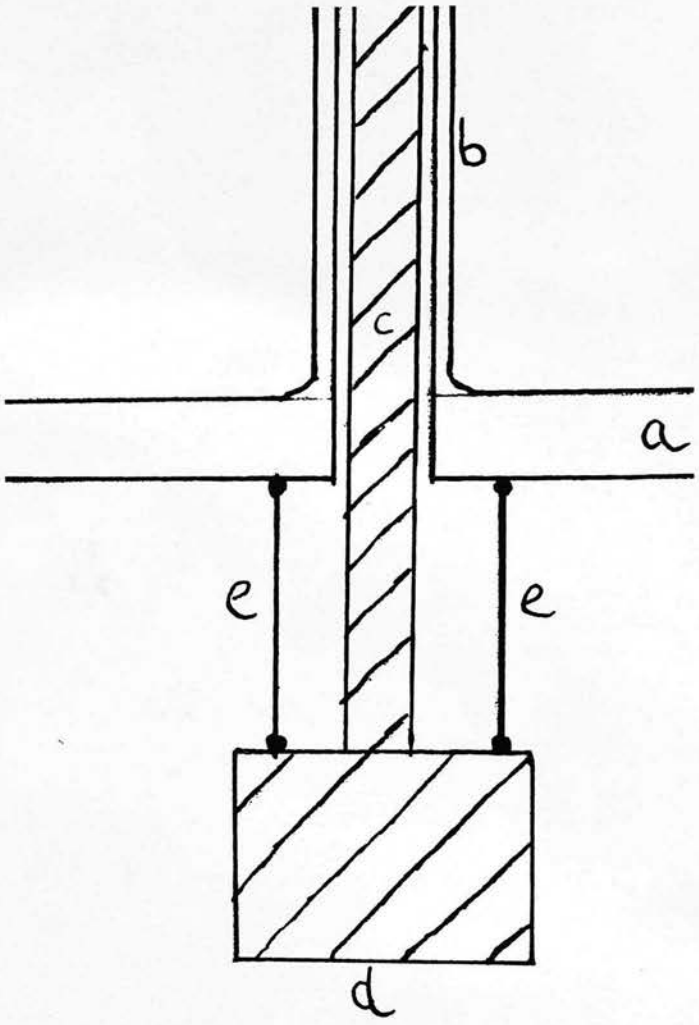


Fig. 2.

Fig. 2 - Diagram of tendon-hammer

a) Horizontal frame

b) Metal tube

c) Rod

d) Weight

e) Elastic Bands

The recording of the ankle jerk:

The jerk was recorded by linking the foot-plate by a non-extensible wire to a stiff cantilever, movement of which was transmitted to the movable anode of a special transducer valve, R.C.A. 5734 (Johns; 1956), the output of which can be led unamplified to a cathode ray oscilloscope. Since it was slightly sensitive to microphonic vibrations which tended to distort the trace, it was shock-mounted with rubber to cut down any microphonics induced by the blow of the hammer. For the same reason, the wire linking the foot-plate to the transducer was coated with rubber.

The electromyographic accompaniment of the muscle twitch was recorded simultaneously by means of electrodes placed over the calf muscles (vide infra) and displayed on the second beam of the oscilloscope.

The electrically induced reflex:

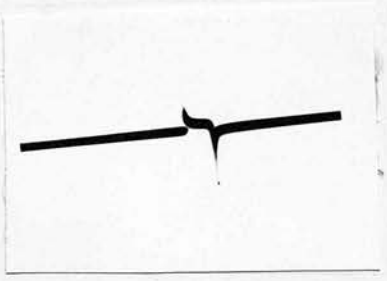
Much of the work was done using the method used first by Hoffmann (1918 - 1952) and recently by Magladery and his colleagues (Magladery et al 1950 a, 1950 b, 1950 c, 1951 a, 1951 b, 1952, 1955; Teasdall et al 1951, 1952 a, 1952 b; Park et al 1951; Languth et al 1952) and by Paillard (1953 a, 1953 b, 1955 a, 1955 b, 1959 a, 1959 b) amongst others.

It is based on the fact that provided certain precautions are taken, it is possible to stimulate the afferent fibres in the medial popliteal nerve and to obtain a reflex contraction of the calf muscles, that is, a sort of ankle jerk which by-passes the muscle stretch receptors.

Paillard (1955 b) has stressed the importance of using wide stimulus pulses of the order of 1 m.sec. and this is in keeping with the well-known physiological fact (Erlanger and Blair 1938; Skoglund 1942; Kugelberg 1944) that sensory fibres have a lower threshold for wide pulses than motor fibres and a higher threshold for short pulses.

It was found important to use a constant current stimulator rather than the constant voltage one favoured by the M.R.C. sub-committee on stimulators (1958). This arises out of a point briefly mentioned in the report of this sub-committee: when a constant voltage stimulator is used, the current flowing through the skin is distorted so that the effective stimulus consists of two brief spikes of opposite polarity separated by an interval during which the current is only a small fraction of the nominal one (figure 3a). When the nominal pulse length is increased, the two spike components move apart but the length of the effective stimulus is not necessarily increased (figure 3b). This effect is not seen with a constant current stimulator (figure 3c,d.).

The stimulator used was that devised by Perkins (1955). Since this is a constant voltage stimulator, it was modified in the following way: a floating, battery operated, constant current output-stage was introduced into the circuit. This had an output impedance of 2 M Ω. The output current could be increased up to a maximum of 15 mA. This device was fed with pulses of variable width (usually 1 m.sec.) from the radio frequency (R.F.) isolating unit of the main stimulator.



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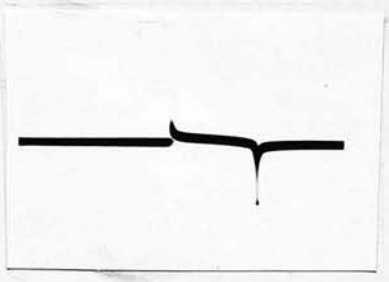

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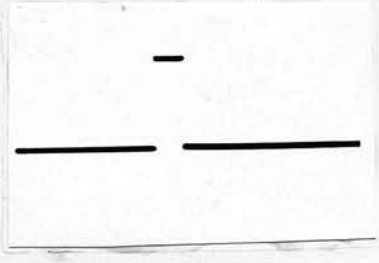

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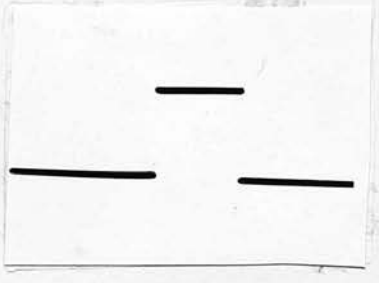


d.

Fig. 3

Fig. 3 - a) Showing the form of the current flowing through the skin as monitored by a sampling resistance when a constant voltage stimulator is used. Nominal pulse length 250 m.secs.

b) As a). Nominal pulse length 1 m.sec.

c) Same as a) with constant current stimulator. Nominal pulse length 250 m.secs.

d) As c). Nominal pulse length 1 m.sec.

The stimulating electrodes used consisted of chlorided silver covered by a pad of lint which was kept moist with saline. The electrodes were fixed on to a plate of perspex, the electrode separation being 3 cms . The plate was strapped over the medial popliteal nerve, the position of the nerve having been previously determined by stimulation. The cathode was situated proximal to the anode, but in practice this arrangement was not found to be critical.

Electrodes applied to the skin surface were used to record the electromyographic responses (E.M.G.) of the underlying muscle. These were preferred to needle electrodes as it was considered that a better assessment of the behaviour of the whole muscle could be obtained in this way. The electrodes were small chlorided silver cups 1 cm in diamter. A pair of these were fixed with adhesive tape to the skin overlying the soleus muscle in the long axis of the leg. The interelectrode distance was approximately 3 cms.
In the early experiments recordings were also taken with a monopolar electrode, the indifferent electrode being placed over the external malleolus. Since the results obtained in this way did not differ appreciably from those obtained with bipolar recording and since the monopolar technique led to difficulties with an inconveniently large stimulus artefact and 50 cycles/sec. interference, this method was abandoned.

A large silver plate placed on the leg between the stimulating and recording electrodes was connected to the common earth point of the recording amplifier. All electrodes were applied to the skin after its resistance had been lowered by the inunction of Cambridge electrode jelly.

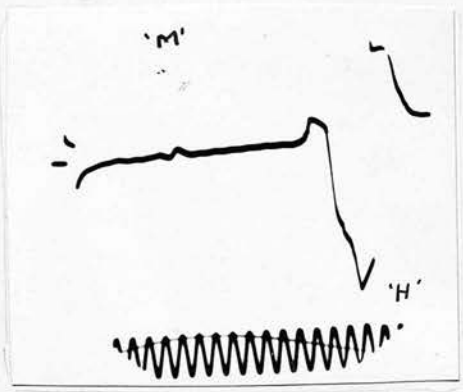
The soleus muscle was used rather than the gastrocnemius because, although there is no clear differentiation between red and pale muscle in man, the soleus appears to play a greater part in reflex contraction. There is evidence that this is true in animals (Denny-Brown 1929; Creed et al 1932; Granit et al 1956; Granit et al 1957; Kuno 1959) and evidence that it may well be true in man in presented in appendix L.

The ouput from the recording electrodes was fed through a standard Ediswan portable E.E.G. amplifier to a cathode ray oscilloscope (overall time constant approximately 0.03, high frequency attenuation 15% at 5 Kc.)

The timing device used was an Ediswan L.F. oscillator R 666.

The type of record that is obtained in normal subjects by a threshold pulse 1 m. sec. long is shown in figure 4 . The base line is displaced at approximately 30 m. secs by a wave (known as the "H" wave). As the current is increased a second wave appears preceding the "H" wave at approximately 5 m. secs after the stimulus. This is known as the "M" wave. These waves have been so named by Magladery et al (1950 a) who have shown that the "M" wave is caused by impulses set up in the muscle by direct stimulation of the motor fibres in the nerve, and the "H" wave by reflex contraction of the muscle set off by stimulation of the afferent fibres. These workers have produced good evidence to suggest that the impulses involved are carried by Group 1 afferents and that the reflex is a monosynaptic one with a synaptic delay of less than 1 m. sec (Magladery et al 1951 a).

At first sight, the large fluctuations (2 - 8 m. secs) in the latency of the "H" wave reported by Magladery et al (1951 a) would seem to conflict with its suggested monosynaptic nature since the fluctuations in latency of a monosynaptic response are always below 1 m. sec (Lloyd 1943 a).



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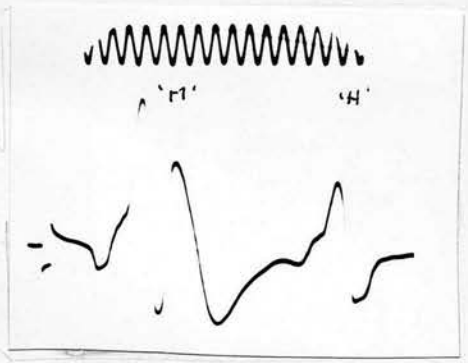

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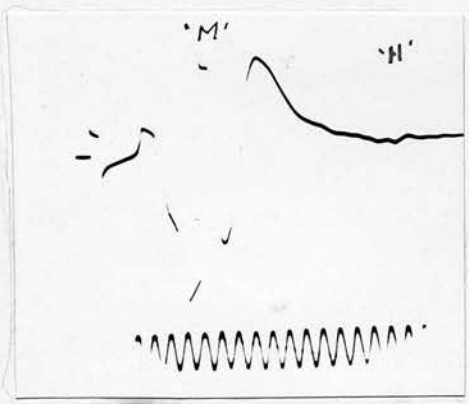


c.

Fig. 4

Fig. 4 - Electromyographic record from a normal subject following stimulation of the medial popliteal nerve.

a) Shows the "H" wave

b) Following an increase in current, the "M" wave appears and the "H" wave diminishes in size.

c) A further increase in current - "M" wave now large, "H" wave has almost disappeared. Time 500 c/s.

However, Paillard (1955 b) has shown that this apparent fluctuation is attributable to the choice of the beginning of the wave as a landmark for timing purposes. He suggests that this is an unreliable landmark as it is affected by a change in the amplitude of the wave. He prefers to use the position of maximal synchronisation of active fibres, i.e. the point of inversion of the biphasic wave. When this landmark is used the fluctuation is never greater than 1 m. sec.

Paillard (1955 b) has also shown that with a sufficiently strong stimulus the electromyograph of the mechanically produced ankle jerk ("T" wave) is identical with the "H" wave so far as shape and duration are concerned. He attributes the difference in latency between the two to the time taken for stimulation of the stretch receptors and to the longer pathway involved in the conduction of the "T" wave.

Hoffmann (1934) has outlined the arguments in favour of the contention that the pathways for the "T" and "H" wave are identical above the knee. This must be accepted as being true in the cat where Lloyd (1943 a) showed that the pathway for stimuli arising in the annulospiral endings of the muscle spindles is the same as that for impulses evoked by electrical stimulation of the afferent fibres with the lowest threshold and highest conduction velocity (Lloyd 1943 b).

Although a larger proportion of inhibitory fibres (originating from tendon-organs and secondary muscle endings) might be involved in the stretch-induced volley, this would not be expected to affect the first reflex response. Impulses leading to autogenetic inhibition of a muscle are carried by Group Ib and Group II fibres and mediated through at least one intercalated neurone (Laporte and Lloyd 1952; Eccles et al 1957 a, 1957 b; Eccles and Lundberg 1959) whereas the stretch reflex is transmitted monosynaptically by Group Ia fibres. Therefore if the first stimulus is adequate it will cause the anterior horn cells to discharge before the inhibitory volley has reached them. To avoid such a possible difference between the mechanically and electrically induced volleys when repeated stimuli were used, care was taken to allow several seconds between each stimulus.

It would therefore seem legitimate to suggest that changes which affect both the "H" wave and the ankle jerk("T" wave) are due to influences directly affecting the motor neurones, while those which affect the ankle jerk only are due to changes in the excitability of the stretch receptors.

At a very early stage in the series of experiments it was decided that any attempt to compare the threshold of the "H" wave of different subjects would be pointless. Variations in the depth of the nerve and in the conductivity of the overlying tissues are enormous, and even in any one subject slight movement of the stimulating electrode can make an appreciable difference to the threshold. Paillard and Turner (1953) and Paillard (1955 b) have suggested that the ratio of the threshold of the "M" wave to that of the "H" wave might provide a useful figure for comparison between subjects. I have found this to be unreliable. In spite of all these objections, providing the stimulating electrodes are kept at the same place, the threshold of the "H" wave remains reasonably constant in <u>any one subject</u>.

Motor nerve conduction studies:

For this part of the experiment, the method described by Simpson (1956) and applied to the lower limb by Gilliatt and Sears (1958) was used.

The stimulating electrodes were applied to the lateral popliteal nerve behind the fibula and to a branch of this nerve, the anterior tibial nerve, at the level of the ankle. The cathode was distal to the anode.

The recording electrodes were the same as those described above. They were fixed over the extensor digitorum brevis muscle by means of adhesive tape. A large metal plate was placed between the stimulating and recording electrodes and connected to the earth terminal of the amplifier.

For each stimulus position, the time between the beginning of the stimulus artefact and the earliest deflection caused by the muscle response was measured. The conduction time between the two sites was obtained by subtracting the smaller from the larger figure. The distances along the line of the nerve between the stimulating cathode and the nearest recording electrode were measured. Where possible, the conduction velocity of the fastest fibres between the two stimulating sites was estimated so that it could be compared with the figures given by Thomas et al (1959) for normal subjects.

The figures given by these workers for the lateral popliteal nerve using the extensor digitorum brevis are Mean 4 9.7 S.D. 7 Range 35.6 - 63.5. Where it was not possible to stimulate at two sites, the result was recorded as a conduction time.

Unfortunately, a similar study of the medial popliteal nerve was not practicable because in most cases only a few centimetres of nerve are available for stimulation. It is therefore impossible to stimulate the nerve at two sufficiently separated sites. The use of the conduction time for this nerve is fraught with pitfalls. This depends on placing the recording electrode on or very near the motor point. Since the muscle used, the soleus, is large, the chances of inaccuracy in the placing of the electrode are high. Even if it is as little as one centimetre away an appreciable error will have been introduced since conduction velocity in muscle (Buchthal et al 1955) is less than 10% of that of nerve.

Magladery et al (1951 a) have in fact obtained figures for conduction velocity in the medial popliteal nerve by stimulating at two sites, but as the two points are only a few centimetres apart, any errors of measurement must be enormous. In fact, this is borne out by the large fluctuations in the figures obtained by these workers.

At an early stage in this investigation and for reasons which will become apparent later, it was found necessary to carry out a certain number of experiments on normal subjects. The methods used will be outlined here and the results reported in the next chapter. These results are crucial to the discussion of the areflexias which follows and comment on them will be reserved for this discussion.

Procaine block of the medial popliteal nerve:

The course of the medial popliteal nerve was plotted by electrical stimulation, monopolar cathodal stimulation being used in this case. The anode was placed over the patella. At any one level, it was assumed that the nerve lay beneath that point which gave the greatest muscle response on stimulation. 5 mls. of 1% procaine were then injected around the lowest accessible part of the nerve. The ankle jerk and "H" wave were tested every minute. A similar quantity of saline was injected in the homologous position on the opposite side. The "H" wave and ankle jerk were elicited at one minute intervals, the electrical stimulation being applied above the site of injection. The procedure was repeated on the next day when the highest available part of the nerve was injected and the stimulating electrodes were over the lowest part of the nerve.

For this part of the experiment six normal subjects were used. These were selected as suitable because they had at least 20 cms of nerve available for stimulation. This was important if the injection was to be carried out at a sufficient distance from the site of stimulation. This requirement considerably limited the number of subjects available as in most cases only about 5 cms of nerve are near enough to the surface to allow stimulation.

Ischaemic block of the medial popliteal nerve:

This method was applied to five normal subjects. The ankle jerk and "H" wave were recorded in the usual way. A sphygmomanometer cuff was then placed around the middle of the thigh and this was inflated to a pressure above the systolic and maintained at that level until the ankle jerk was abolished. Again, the ankle jerk and "H" wave were elicited at one minute intervals in the first three cases and at ½ minute intervals in the remainder. The cuff was then released and the testing continued for a further 15 - 20 minutes.

Results of experiments on normal subjects

1) The electrically induced reflex:

Fifty normal volunteers were examined by this method. These were either medical students or young patients with no abnormalities of the tendon reflexes. Their ages fell between 13 and 35 years, old patients being excluded as they have been shown (Birren and Wall 1956; Magladery 1959; Magladery et al 1960) to have changes in the peripheral nerves and the reflex arc.

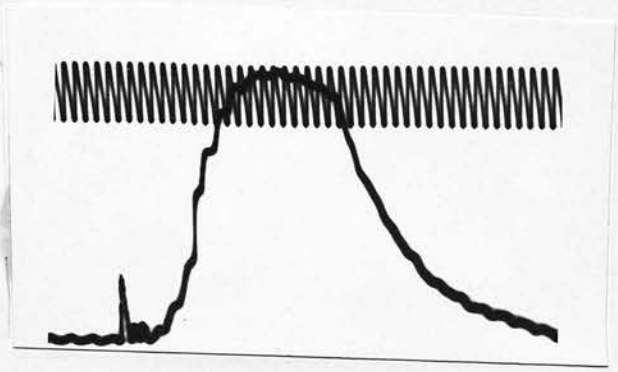
Under the conditions I have described, "H" waves were obtained without difficulty from everyone of these subjects.

2) Dilute procaine block:

Six subjects selected as outlined above were used in these experiments. Within ten minutes of the injection the ankle jerk (and "T" wave) had disappeared although there was no change either in the threshold or in the amplitude of the "H" wave (figure 5).

When saline was injected, no effect was observed in either the "H" wave or the reflex.

The same results were obtained on the next day when the nerve was stimulated below the site of injection,



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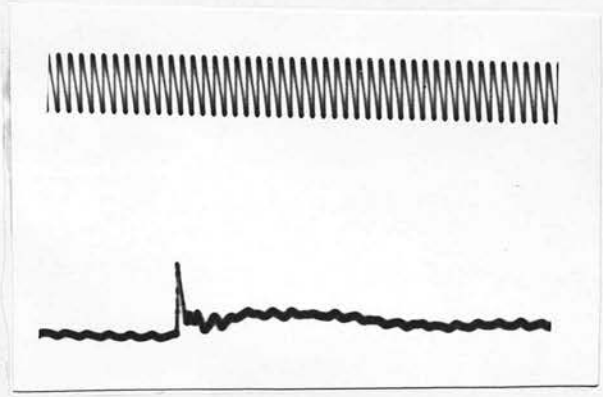

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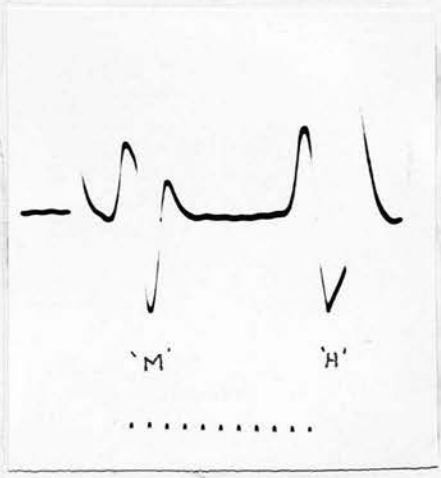


c.

d.

Fig. 5

Fig. 5 - Normal subject.

a) Recording of ankle jerk before procaine infiltration. Time 100 c/s.

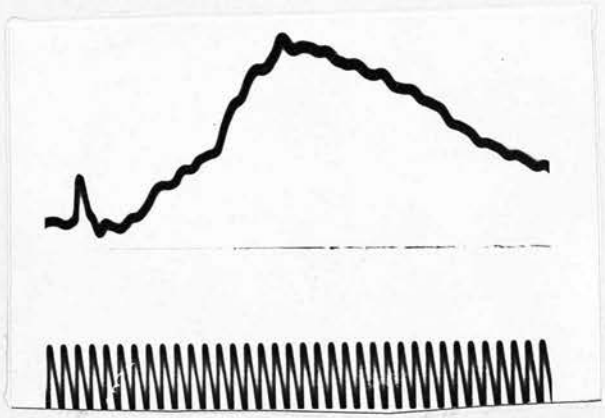
b) Ankle jerk after infiltration of 5 mls of 1% procaine around the medial popliteal nerve. Time 100 c/s.

c) The "M" and "H" waves before procaine infiltration. Time 500 c/s.

d) The "M" and "H" waves after procaine infiltration. Time 500 c/s.

Ischaemic block:

The ankle jerk and the "H" wave both showed a diminution in amplitude almost simultaneously. Both disappeared within 15 minutes of inflation of the cuff. When the pressure was released they both returned together at about the tenth minute. At no time when the ankle jerk was absent was the "H" wave obtainable.



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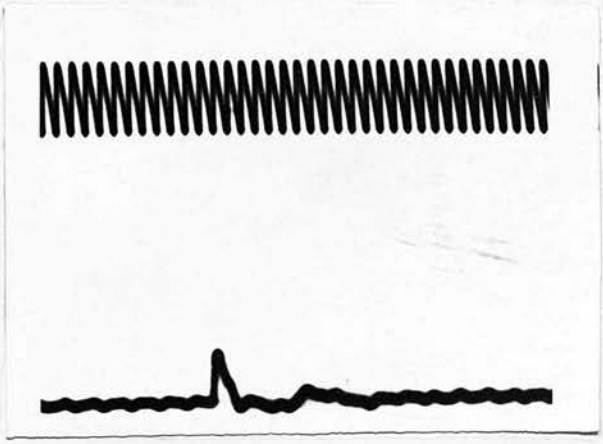

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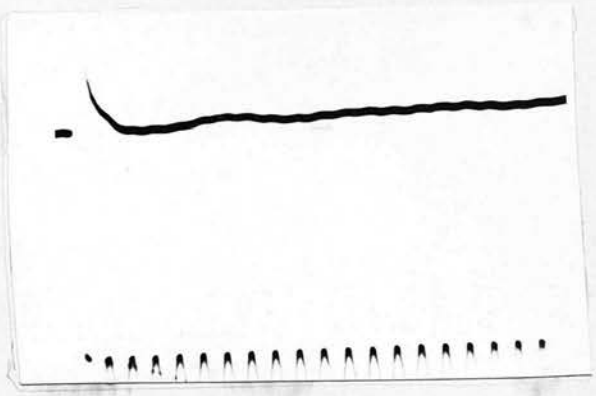


d.

Fig. 6

Fig. 6 - Normal subject.

a) Recording of ankle jerk before inflation of sphygmomanometer cuff placed around the thigh. Time 100 c/s.

b) Same 15 minutes after inflation of cuff. Time 100 c/s.

c) "M" and "H" wave before inflation of cuff. Time 500 c/s.

d) Same after inflation of cuff for 10 minutes.

The Areflexias

The tendon reflex could, theoretically, be affected by a lesion in any of the following sites:

1) The stretch receptors
2) The peripheral nerves (afferent fibres)
3) The posterior nerve roots
4) The synapses in the spinal cord
5) The anterior horn cells (alpha-motorneurones)
6) The anterior horn cells (gamma-motorneurones)
7) The anterior nerve roots (alpha-efferent fibres)
8) The anterior nerve roots (gamma-efferent fibres)
9) The peripheral nerves (alpha-efferent fibres)
10) The peripheral nerves (gamma-efferent fibres)
11) The motor end-plates
12) The extra-fusal muscle fibres
13) The supraspinal facilitatory pathways

Most explanations of the loss of tendon reflexes are based on an assumed lesion in 2) or 3). Occasionally 5), 7), 9) and 12) are considered in patients who are very weak. This study is an attempt at finding out whether abnormalities in the other regions can in practice cause a loss of tendon reflexes.

Part 11: The Areflexias:

1) Friedreich's Ataxia

Introduction:

In 1861 Friedreich of Heidelberg described a case of the disease which now bears his name. Two years later in a paper entitled "On degenerative atrophy of the dorsal columns of the spinal cord" he gave a detailed clinical and pathological account of a further 6 cases.

Neurologists were slow to accept the disease as an entity, for instance we are told (Greenfield 1954) that it was not until 1884 that Charcot accepted it as such, obsessed as he was by its resemblance to disseminated sclerosis. Others failed to distinguish it from "locomotor ataxia".

Many important studies, e.g. Greenfield (1954), have thrown doubt on the validity of the orthodox classifications of the hereditary ataxias. Neverthless, the name Friedreich's ataxia has persisted.

For the purposes of this thesis I have accepted the classification of the spinocerebellar degenerations which Greenfield (1954) has adapted from Zülch (1936, 1948) and which is given below:

A. Predominantly spinal forms

1) Friedreich ataxia
   a) Pure forms
   b) Associated with peroneal atrophy (hereditary areflexic dystasia of Roussy and Lévy 1926, 1934 or familial claw-foot with absent tendon jerks of Symonds and Shaw 1926)
   c) Posterior column ataxia

2) Hereditary spastic ataxia

3) Hereditary spastic paraplegia

B. Spinocerebellar forms

1) Marie type of hereditary ataxia (olivopontocerebellar degeneration)

2) Subacute spinocerebellar degeneration (carcinogenic and sporadic)

C. Cerebellar forms

1) Holmes type of hereditary ataxia

2) Diffuse atrophy of Purkinje cells

We are only concerned here with the predominantly spinal forms and among these forms only those cases with absent reflexes, that is, the "pure" cases of Friedreich ataxia and those with associated peroneal muscular atrophy.

It is probable that between the "pure" form of Friedreich's ataxia and the pure peroneal muscular atrophy there exist a large number of cases with varying degrees of involvement of peripheral nerves.

In this section I intend to deal with only the "pure" cases of Friedreich's ataxia, that is, those with no muscular wasting other than can be accounted for by disuse atrophy and no exteroceptive sensory loss. The other "mixed" group will be discussed separately because there is reason to believe that the areflexia has a different mechanism in these cases.

Friedreich's ataxia, to quote Greenfield and Blackwood (1958) 'has come to be recognised as one of the most common hereditary disorders of the nervous system'. It has been studied extensively from the clinical and pathological points of view, but one important feature of the condition remains unexplained - the early loss of the ankle jerks.

Most writers on the subject are elaborately vague about this. For example, one well-known textbook of neurology (Russell Brain 1955), after describing the pathology as consisting of degeneration of the corticospinal, spinocerebellar tracts and posterior columns, states 'the tendon jerks are lost because of interruption of the reflex arc on the afferent side'. The reflex arc does not, of course, involve any of the structures named. There are in fact some changes in the dorsal roots but these appear to be minor and no writer has laid much stress upon them. I do not think that they can wholly explain the profound and early areflexia so characteristic of the condition.

Material: Eight cases of "pure" Friedreich's ataxia were studied.

Methods: The methods used to investigate these cases have already been described. They were:-

1) Motor nerve conduction studies carried out on the lateral popliteal nerve
2) Recording of the response to mechanical stimulation
3) Stimulation of the afferent fibres of the medial popliteal nerve.

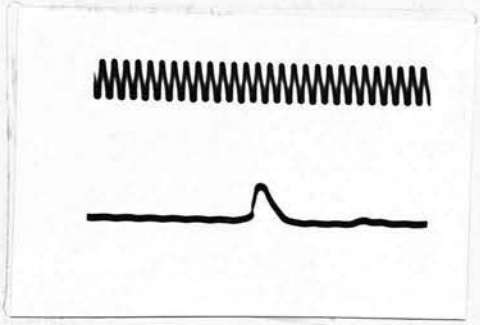
Results: 1) Motor nerve conduction: Table 1 shows that the results obtained are within the normal limits given by Thomas et al (1959) for the lateral popliteal nerve to extensor digitorum brevis (Mean 49.7 metres per sec. S.D. 7.1 Range 35.6 - 63.5 metres per sec.

Table 1:

The conduction delay at the extensor digitorum brevis following stimulation at the knee and ankle, and the estimated conduction velocity in 8 cases of Friedreich's ataxia.

Case	Delay with stimulation at knee (m.secs)	Conduction distance (cms)	Delay with stimulation at ankle (m. secs)	Conduction distance (cms)	Velocity (metres per sec)
W.H.	12	42	5	8.5	48
J.McL.	9.5	44	3.5	9	58.3
N. McL.	9	39.5	4	8.5	62
M.H.	10	34	3	7	39.1
A.H.	9	29	4	6.5	45
B.H.	12	35	4.5	8	40
D.A.	11.5	43	4.5	8	50
R.A.	12	40.5	4	7	41.8

2) No jerk (or "T" wave) was recordable from any of the cases - figure 7



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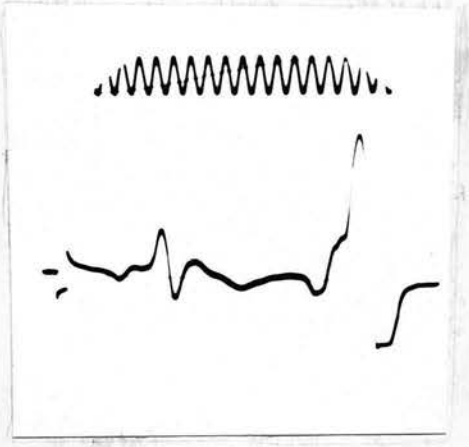


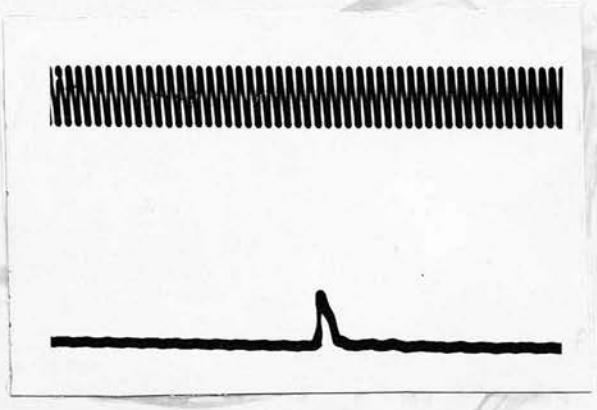
b.

Fig. 7.

Fig. 7 - Patient suffering from Friedreich's ataxia.

a) Tension recording demonstrating the absence of a tendon jerk. The record shows a shock artefact only. Time 100 c/s.

b) "M" and "H" waves recorded from this patient. Time 500 c/s.



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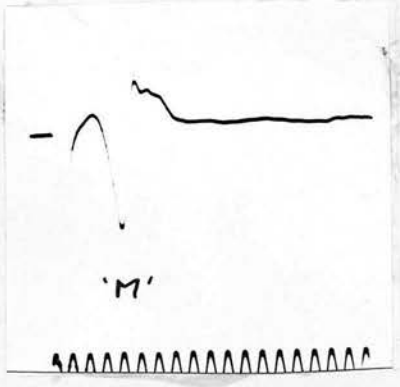


b.

Fig. 8

Fig. 8 - A patient suffering from tabes dorsalis.

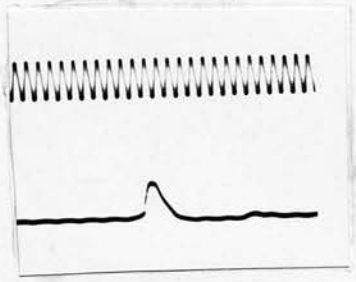
a) Tension recording demonstrating the absence of a tendon jerk. Time 100 c/s.

b) Recording from the calf muscle showing an "M" wave but no "H" wave. Time 500 c/s.

3) The "H" wave was obtained without difficulty in every case tested - figure

The threshold and latency of the "H" wave were not accurately estimated for reasons which have already been given, but they were not markedly different from those found in normal subjects.

These results were in contrast with the findings in 7 cases of tabes dorsalis and 7 cases of peripheral neuropathy also with no ankle jerks. Here, "M" wave was obtained but no "H" waves - figure 8 . They were also different from those in 3 cases of motor neurone disease and two cases of muscular dystrophy with marked wasting, weakness and absent ankle jerks. In these neither "M" nor "H" wave was recordable - figure 9 .



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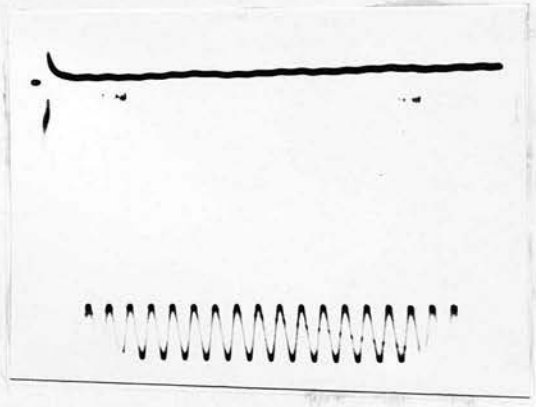


b.

Fig. 9.

Fig. 9 - A patient suffering from motor neurone disease, with severe weakness.

a) No tendon jerk

b) No "M" or "H" waves.

DISCUSSION

These experiments seem to suggest that in Friedreich's ataxia and possibly in some other cases, the stretch receptors lose their sensitivity although the afferent pathway is still capable of conducting impulses to the spinal cord and evoking a reflex contraction of the muscles.

One possible explanation is that there may be some primary disturbance of the muscle spindles themselves. This, however, seems unlikely because as far as we know, skeletal muscle is not primarily affected in Friedreich's ataxia. I have not had the opportunity of obtaining a muscle biopsy from such patients.

The notion that "the general facilitatory and inhibitory systems of the brain stem are instrumental in determining the level of tonic discharge through the spindle loop as well as switching it on and off" (Granit 1955) has received some support from the work of Granit and his colleagues. Granit's conception of the innervation of skeletal muscle is now well-known. It is summarised by the diagram shown in figure 10. It provides a plausible explanation for the situation in Friedreich's ataxia.

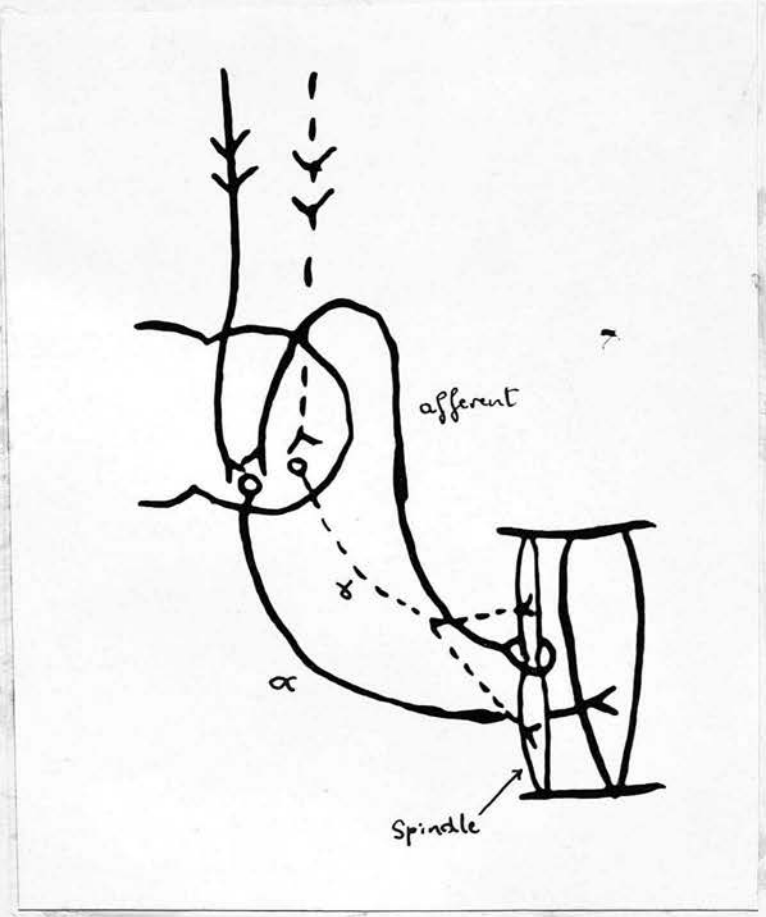


Fig. 10.

Fig. 10 - Diagram from Granit (1955).

Dotted line indicates the gamma-pathway.

Unbroken line indicates the alpha-pathway and the afferent fibres from the muscle spindles.

It has been shown (Granit and Kaada: 1952) that in cats, at any rate, there is tonic firing in the gamma fibres and that this is to a large extent controlled by supraspinal influences. Is it possible that when these are permanently withdrawn by a lesion in the pathway, the gamma motor neurones cease to regulate the muscle spindles which ultimately become insensitive?

We have some information about the behaviour of de-efferented spindles. For instance, Eldred, Granit and Merton (1953) in their work on single spindle afferents have noted that whereas the normal spindle shows tonic discharge at rest, the de-efferented one is silent at rest, has a higher threshold to stretch, and adapts considerably - the rate of firing having been more than halved after half a minute of stretch at a constant tension.

The observation that the net effect of the afferent discharge from a passively stretched de-efferented extensor muscle is largely inhibitory to the homonymous alpha (Henneman 1951; Hunt 1952) and gamma motorneurones (Hunt 1951) makes it appear that some degree of intrafusal muscle tone may be a prerequisite for the very existence of a stretch reflex. The procaine experiments already described tend to confirm this.

As early as 1919 Liljestrand and Magnus had shown that the stretch reflex in cats could be abolished by intramuscular procaine, and in 1947 Sarnoff and Arrowood produced a differential spinal block with procaine - that is, the abolition of reflexes with no change in motor power or proprioception.

Leksell (1945) suggested that the gamma fibres were more sensitive to procaine than the large alpha efferents. This was confirmed by Matthews and Rushworth (1957) who also showed that the stretch reflex and tendon jerk could be paralysed at a time when the motor response of the muscle was otherwise unchanged.

There is, therefore, reasonably good evidence from both human and animal experiments that blocking of the gamma efferents can abolish the tendon jerk by making the spindles insensitive to stretch without interfering with the afferent pathway proximal to them.

These were all acute experiments. It would be interesting to know something of the behaviour of spindles which have been de-efferented for a long time. I have only been able to find one reference to this. Tower in 1932 described the histological changes in muscle spindles following section of the anterior root. At first atrophy occurred solely in the polar regions of the spindles but eventually the equatorial regions became affected.

There remains one possible alternative explanation that might fit the results. It may be argued that a partial lesion in the afferent loop of the reflex arc may allow the well-synchronised impulses produced by electrical stimulation to pass while interfering with the rather more dispersed ones produced by mechanical means. This is unlikely in view of the results of the cuff experiment. Ischaemia first affects the large afferent fibres and produces an increasing block in these. Here, both the ankle jerk and the "H" wave disappeared and reappeared simultaneously.

So far I have concentrated on what I might call the 'peripheral' part of the argument. I have presented evidence suggesting that spindles which have been de-efferented eventually become insensitive to stretch. The weakest part in my argument is the suggestion that with the withdrawal of supraspinal excitatory influences the gamma-motorneurones cease to fire. The only personal evidence I have for this is indirect - the cases with brain stem lesions who lost their ankle jerks (see section on disseminated sclerosis).

In fact abolition of tendon reflexes in patients with supraspinal lesions or lesions well above the particular segment involved in the jerk is not unknown.

Gayer-Morgan and Symonds (1927) described 2 cases of "a forme fruste of encephalitis lethargica with anisocoria and absent ankle jerks" and Brain (1958) in a review of the Physiological Basis of Consciousness refers to a patient who sustained a severe head injury and had a complete loss of ankle jerks and an almost complete loss of knee jerks. Later necropsy revealed necrosis of the tegmentum of the mid-brain. Landau and Clare (1959) in their discussion of "The Human Plantar Reflex" give a report of a case of spinal injury with a lesion at T 10 - 11 and absent lower limb jerks but extensor plantar responses. It therefore seems likely that this sort of disturbance can occur. That it does occur in Friedreich's ataxia can only be inferred.

It is not yet clear whether the supraspinal control of the gamma motorneurones is mediated by way of the Reticulo-Spinal Facilitatory system investigated by Magoun and Rhines (1946) at a time when the existence of fusimotor fibres was just being discovered (Leksell 1945).

In the present state of knowledge it would be unwise to say definitely whether in Friedreich's ataxia there is an irritative lesion which is actively inhibiting the gamma-motorneurones or whether the effect is produced simply by withdrawal of facilitatory impulses. However, it seems unlikely that a lesion would remain irritative for so many years. A destructive process interfering with facilitation appears more likely.

Gilliatt (1961) has been studying this problem from a different point of view. In his cases of Friedreich's ataxia he has found it impossible to record nerve action potentials from the lateral popliteal nerve with stimulation at the ankle. He suggests that there is a peripheral nerve involvement and that this is responsible for the loss of ankle jerks. I do not think that his interpretation is valid because:

1) His cases were not "pure" cases of Friedreich's ataxia. They showed muscle wasting and blunting of superficial sensation. This type of case has been excluded from my series because the loss of tendon jerks could have a peripheral cause which is not applicable in "pure" Friedreich's ataxia.

2) The technique of recording sensory action potentials from the lateral popliteal is an extremely difficult one. The signals recorded from normal subjects are of the order of a few microvolts and failure to record them cannot without further confirmation be considered as incontrovertible evidence of peripheral nerve involvement. Writing about nerve action potentials recorded from the ulnar nerve where the signal is usually about ten times that in the lateral popliteal Gilliatt (1958) remarks that the action potentials "were always small and in some obese but otherwise

small and in some obese but otherwise normal subjects they were altogether absent". If this is true of the ulnar nerve is it not even more likely to be so of the lateral popliteal?

3) He used a constant current stimulator which may not have given wide enough pulses to stimulate the sensory fibres.

4) It is the medial, not the lateral popliteal nerve that is concerned with the ankle jerk. It does not necessarily follow that because the lateral popliteal is involved, the medial popliteal should be affected as well.

There is further additional though rather circumstantial evidence against the view that changes in the peripheral nerves are responsible for the loss of tendon reflexes in Friedreich's ataxia. There were no changes in motor nerve conduction such as those that have been described by Simpson (1958) and others in peripheral neuropathies. This, taken with the lack of any exteroceptive sensory loss suggests that any involvement of peripheral nerves must be strangely selective, affecting the large sensory fibres and sparing both the large motor and the smaller sensory fibres.

It would be of considerable value to be able to find out more about the afferent side of the reflex arc. Magladery (1950 a) did estimate the conduction velocity on the afferent side by stimulating at two levels. I have attempted to do this but since, in most cases, the length of medial popliteal nerve available for stimulation is limited to a few centimetres, the difference in latencies is so small and the possibilities of error so high that consistent results cannot be obtained.

At any rate, the latency of the "H" wave in my cases was always of the order of 30 m. secs - the same as that found in normal subjects (Magladery 1950 a, Paillard 1955 a, 1955 b) so that there was certainly no gross slowing of conduction around the reflex arc.

A further refinement of the technique of recording nerve action potentials may eventually give more direct evidence about the state of the large afferent fibres.

My results do not exclude the possibility that changes in the posterior root or peripheral nerves may contribute to the absence of tendon jerks in Friedreich's ataxia, but it is submitted that such changes can not account for the striking loss of jerks with retention of the "H" wave in "Pure" cases of Friedreich's ataxia and I suggest that an important contributory factor may be a withdrawal of excitatory influences which normally travel down the gamma-system.

This would adequately account for the retention of the "H" wave (indicating patency of the major part of the reflex arc) with loss of reflex excitability to abrupt muscle stretch.

MIXED FORMS

Introduction:

The association of Friedreich's ataxia with clinical signs pointing to peripheral nerve involvement is well-known although comparatively few cases have been described.

Byrom Bramwell (1893) in his Atlas of Clinical Medicine described two examples - brothers who had Friedreich's ataxia and wasting of small hand muscles and "main-en-griffe". Other early descriptions included those of Whyte (1898), Baumlin (1901) and Mott (1907). Between 1910 and 1953 a number of families with Friedreich's ataxia and peroneal muscular atrophy were reported, although in no member of these families were the diseases combined (Spiller 1910; Biemond 1928; Gallotti 1928; Ross 1942; Roth 1948; Pappworth and O'Mahony 1954).

A rather milder form of this condition was described by Roussy and Levy (1926) who coined the term 'hereditary areflexia dystasia'. They insisted that the disease was a separate entity although this was strongly denied by others. Rombold and Riley (1926) recognised its relationship to Friedreich's ataxia while Symonds and Shaw (1926), and more recently Jequier (1948) considered it as a variant of peroneal muscular atrophy.

These cases show a great variety of symptoms and signs. In addition to the features of Friedreich's ataxia such as pes cavus, unsteadiness of gait, clumsiness of the hands, nystagmus (van Bogaert and Moreau 1939), dysarthria (Spillane 1940) and extensor plantar responses, there is wasting of the muscles below the knee and this sometimes spreads to the thigh and is often associated with exteroceptive sensory loss.

Since there is apparent involvement of the peripheral nerves in these cases, it may be that this at least contributes to the loss of tendon reflexes. The experiments which will be described below were undertaken in order to find out whether the areflexia could be completely explained on this basis.

Material:

Seven cases belonging to this group were used for this part of the study. The case histories varied considerably but all had absent ankle jerks, extensor plantar responses and some evidence of peripheral neuropathy such as excessive wasting and/or exteroceptive sensory loss. The full case histories are given in the appendix.

Methods:

1) Conductivity studies on the lateral popliteal nerve: to obtain a measure of the conduction velocity between two points on this nerve. In most cases this was impossible because there was no response from the muscles even when stimulation was pushed to the limits of tolerance. In one case an attempt was made at stimulating the nerve through a needle pushed into it or in its immediate vicinity. At first, a concentric needle electrode of Adrian and Bronk type was used. Later monopolar stimulation through an insulated sewing needle bared at the tip was used. In one case stimulation of the lateral popliteal nerve at the knee in the ordinary way did produce a response from the extensor digitorum brevis muscle although stimulation at the ankle had no effect. In this case the result was expressed as a conduction time.

2) Medial popliteal nerve stimulation: this was carried out in every case in an attempt to record "H" waves by the method described in previous sections.

Results:

1) Lateral popliteal stimulation: In 6 cases (Mgt. M., R. McK., F. McK., M.H., M.C., K.McL.) stimulation whether at the knee or ankle with pulses exceeding 15 mA and 4 m. secs duration produced no response from the extensor digitorum brevis. Stimulation through a needle was also ineffective in the single case investigated by this method.

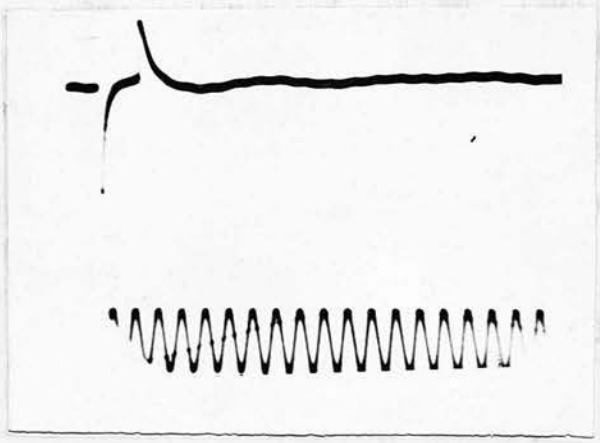
In one case (W.P.) only stimulation at the knee produced a response in the muscle, although this was small and very dispersed. The figure for the shortest latencies are therefore given. These were:

Right leg - 50 m.secs for a distance of 40 cms

Left leg - 33 m.secs for a distance of 40.5 cms

Although these figures cannot be compared with those given by Thomas et al (1959) for conduction velocity in normals, it seems reasonable to assume that they are highly abnormal since the larger one is over four times the highest figure for latency usually obtained in normal subjects and in patients with Friedreich's ataxia (12 m. secs).

In those cases showing no response to stimulation of the lateral popliteal nerve, the skin electrodes were left in the same position and the patient was asked to extend his toes. In every case, voluntary action potentials could be recorded from the extensor digitorum brevis muscle indicating that it was not completely denervated.



Ca.

b.

Fig. 11

Fig. 11 - A patient with the Roussy-Levy syndrome.

a) Electromyographic record obtained from electrodes placed over the extensor digitorum brevis. The record shows no response to stimulation with a large wide pulse. Time 500 c/s.

b) Electrodes in the same position. Effect of a voluntary contraction. Time 100 c/s.

2) Medial popliteal nerve stimulation: No "H" wave was recordable in any of the cases. In most patients there was no "M" wave either but in two (W.P. and F. McK.) a very small and dispersed "M" wave was found.

Discussion:

These results seem to suggest that in this group of cases the peripheral nerves are affected to an extent which is quite sufficient to interfere seriously with the reflex arc. The absence of the "H" wave in every case, the unusually great difficulty in stimulating the nerves, and the severe depression of nerve conductivity seem to warrant this conclusion.

The mechanism by which these lesions in the peripheral nerves interrupt the reflex arc is still subject to speculation. It is possible that the nerve lesion constitutes a block which does not allow impulses to pass or, alternatively, that it 'desynchronises' the volley, spreading it out so that at any one instant there is an insufficient number of impulses arriving at the anterior horn cells to stimulate them. That such a desynchronisation does occur on the motor side is clear from the appearance of the action potential that is recorded from the muscle when it does respond to stimulation of its nerve. It seems reasonable to assume that this also occurs on the afferent side. Both factors could, of course, combine to cause the areflexia.

The lack of response to stimulation is puzzling in view of the fact that action potentials associated with voluntary contraction could be recorded from the extensor digitorum brevis muscle. It is as though the nerve were insulated but still capable of conducting impulses. Such a lack of response to stimulation was noted by Déjerine and Sottas (1893) and Déjerine (1896) in their original descriptions of hypertrophic polyneuritis.

This raises the point that it is extremely difficult to distinguish clearly between hypertrophic polyneuritis, peroneal muscular atrophy and Friedreich's ataxia.

Marinésco (1894); Raymond (1906); Long (1912) and Hoffmann (1912) were all in favour of considering hypertrophic polyneuritis as a variety of peroneal muscular atrophy. Achard and Thiers (1924) divided their cases into two groups: 1) The Déjerine-Sottas type - tabetic type symptoms were superimposed on those of peripheral neuritis. 2) the Pierre Marie-Bovéri type where the peripheral features were complicated by a 'cerebellar' type of picture. Villaret et al (1935) pointed out how easy it was to confuse hypertrophic polyneuritis with Friedreich's ataxia or peroneal muscular atrophy if the peripheral nerves are not palpated, and they quoted Austregesil (1930) as considering all three diseases to be related.

Certainly a careful examination of the literature on hypertrophic polyneuritis makes it difficult to refute this view. For example, a large number of cases have been reported as having extensor plantar responses (Achard and Thiers 1924; Sears 1931; Russell and Garland 1930; Villaret et al 1935; Luban 1951; Roger et al 1952). Nystagmus is not uncommon and was reported in Déjerine's original cases (Déjerine and Sottas 1893; Déjerine 1896) and in many cases since (Rossolimo 1898; Higier 1926; Russell and Garland 1930; Villaret et al 1935; Schaller and Newman 1935). Dysarthria and intention tremor may occur (Déjerine and Sottas 1893; Déjérine 1896; Marie 1906; Roussy and Cornil 1919; Wolf et al 1932). Pes cavus was present in over one third of Austin's (1956) series and kyphoscoliosis in one fifth of Schaller and Newman's (1935).

In hypertrophic polyneuritis,as well as the classical 'onion-bulb' formation of the nerve sheath, there are marked interstitial changes which are variously described as 'mucoid','myxoedematous', 'gelatinous' , and which are largely responsible for the enlargement of the nerves. This tissue which is rich in mucopolysaccharides (Austin 1956) would form a very effective insulating layer. This might explain the findings in the stimulation experiments. The possibility

that during voluntary contraction, the electrodes were recording action potentials from relatively spared neighbouring muscles innervated through branches of the medial popliteal nerve can probably be discounted since this was not found in cases of pure lateral popliteal palsy.

The dramatic slowing of the conduction velocity is in keeping with the results already reported by Gilliatt and Sears (1958) in two cases of familial hypertrophic polyneuritis and in two cases of peroneal muscular atrophy, and by Christie (1961) in a group of cases of peroneal muscular atrophy. While it is not my intention to discuss at any length the reason for this slowing, one rather attractive, though speculative possibility springs to mind: that the swelling of the myelin sheaths and the presence of thick impermeable interstitial tissue 'occlude' the nodes of Ranvier and that conduction along the nerve ceases to be saltatory. This effect could also be caused by demyelination. Alternatively, the slowing might be contributed to by the earlier and more rapid disappearance of the larger fibres which is known to occur in many of these conditions (Austin 1956).

Whatever the answer to these problems may be, it is obvious that the changes in the peripheral nerves must be largely responsible for the loss of tendon jerks in these 'mixed' forms of Friedreich's ataxia. The loss of the H-reflex pari passu with the loss of tendon jerks

in in contradistinction to its retention in the 'pure' form of Friedreich's ataxia described earlier.

DISSEMINATED SCLEROSIS

Loss of ankle jerks occurs only rarely in disseminated sclerosis. Sometimes this occurs in patients who have been bed-ridden for many years and who have developed contractures which make plantar flexion of the foot impossible, sometimes the foot is already in extreme plantar flexion,and sometimes the loss of jerks is associated with almost constant flexor spasms or flexion contracture, the Achilles tendon becoming so taut that appreciable stretching by a tendon-hammer becomes impossible. It is also conceivable that autogenetic inhibition from a constantly stretched muscle may play a part.

Such cases are probably not very common.. I have not seen any during the period of this study but I have seen three cases of disseminated scleroris with loss of ankle jerks where these factors could not be invoked.

Material:

1) The first case is particularly interesting because the clinical signs allowed a reasonably accurate localisation of the plaque and because the disturbance was transient, allowing the patient to act as her own control.

She was a 16 year old girl with an acute demyelinating condition and signs indicating a lesion in the left side of the medulla oblongata. She had poor co-ordination in all limbs and depression of tendon reflexes. The ankle jerks were abolished and the right plantar response extensor. Sensation in the limbs was normal. The brain stem signs receded rapidly while she was being treated with prednisolone and the ankle jerks returned.

2) The second case presented a rather similar problem. A young woman of 25 developed sudden blurring of vision in the left eye and subjective numbness over the left side of the face and body. The left optic disc was found to be swollen. The left ankle jerk was sluggish and the right absent. Both plantar responses were extensor. Following treatment with A.C.T.H. her condition improved and the ankle jerks returned.

In the third case it was unfortunately impossible to localise the lesion accurately but here again the ankle jerks were absent though both plantar responses were extensor.

Full case histories for all three cases are given in the appendix.

Methods:

Stimulation of the medial popliteal nerve and recording of the ankle jerk.

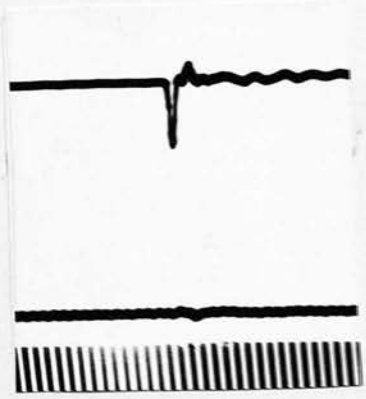
Results:

During the acute stage of the disease no tendon reflex could be recorded from cases 1 and 2. The jerk was absent throughout in case 3. In all three cases the "H" wave was present.

Discussion:

These cases have already been referred to in the discussion on Friedreich's ataxia. The importance of the first two lies in the fact that there was good clinical evidence suggesting a lesion on the brain stem and that the loss of tendon jerks was transient, the patients acting as their own controls.

All three cases further illustrate the fact that loss of tendon reflexes can occur following a lesion at a site well above the segmental level involved in the particular reflex arc.



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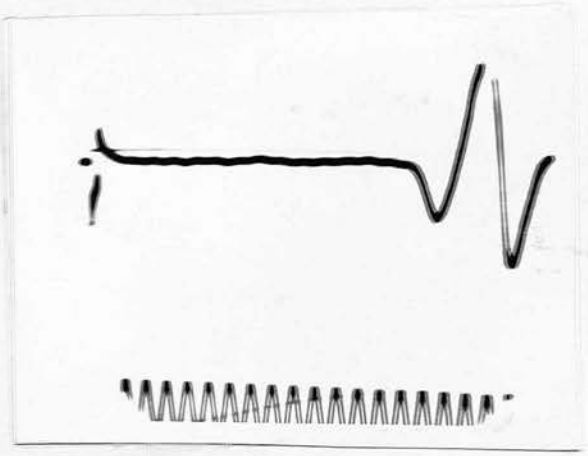

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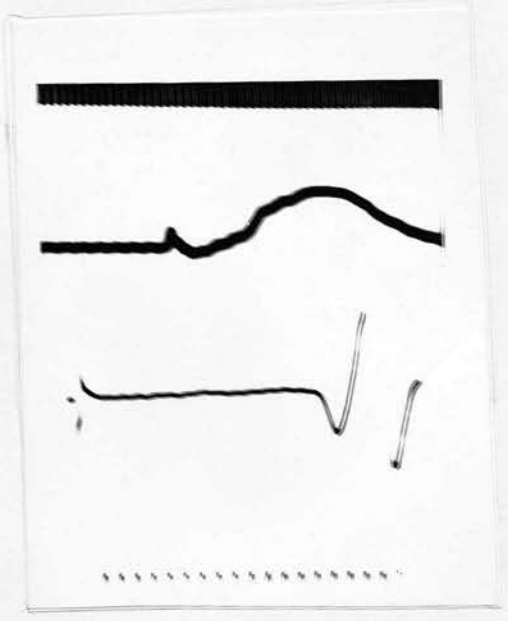


c.

Fig. 12

Fig. 12 - M.S. - a patient with a demyelinating lesion in the brain stem.

a) Tension recording (top trace) and E.M.G. recording showing the absence of the tendon jerk. Time 100 c/s.

b) The "H" wave recorded from this patient

c) The ankle jerk (top trace) and "H" wave (bottom trace) after recovery.

CEREBELLAR LESIONS

It is generally agreed that lesions in the cerebellum and posterior fossa may be responsible for abnormalities of the tendon reflexes. The most widely known abnormality is the so-called 'pendular' knee jerk. This was described by Gordon Holmes in his Croonian Lectures (1922) and it is usually attributed to hypotonia and the lack of contraction in the antagonists to the prime movers in this reflex (Dow and Moruzzi 1958). As a result the extremity goes through several pendular oscillations after the reflex is elicited. Dow and Moruzzi (1958) state that the division of the cerebellum primarily affected is the lateral part of the posterior lobe of the corpus cerebelli. This often quoted abnormality (the pendular jerk) is not very common. Keschmer and Grossmann (1928) found it in four patients only out of a series of 29 unselected cases of cerebellar disease.

A much commoner abnormality is probably a depression or abolition of the tendon reflexes on the homolateral side. This was noted by Gowers(1892) in cases of tumours of the cerebellum and was mentioned on several occasions by Gordon Holmes (1904 and 1922). The 1904 paper written with Grainger Stewart states "the variability of these reflexes is one of the most striking signs of cerebellar lesions. In unilateral cerebellar tumours, diminution on the side of the lesion is perhaps

is perhaps the most common condition'. The point was also made by Purves-Stewart and Worster-Drought (1952), by Kinnier Wilson (1955 a) and more recently by de Jong (1958) in his book on neurological examination.

The pathogenesis of this areflexia has received little attention, although it was the subject of a controversy between Philippe and Lejonne (1904) and van Gehuchten (1904). The former, backed by Raymond, attributed it to the curious degeneration of the posterior roots which may sometimes occur in cases with increased intracranial pressure, while the latter postulated the loss of an influence normally exerted on the motor-neurones by 'fibres other than the corticospinal'. He believed that this was probably mediated by the rubrospinal tracts. Van Gehuchten's main objection to Philippe and Lejonne's suggestion was that the posterior root changes were minimal and certainly not sufficient to interfere with cutaneous reflexes or proprioception.

In view of the importance now ascribed to the cerebellum in the regulation of the gamma motorneurones (Granit 1955; Granit et al 1955) I felt that the methods described above could be applied with benefit to this problem.

Material:

Three of the subjects were patients who had been operated on for relatively benign cerebellar tumours. They were traced by an inspection of the records of a neurosurgical unit. Cerebellar tumours are often very malignant and many of the patients which, on the basis of case-records seemed to have been suitable for inclusion in this study were found to have died. Others had returned home and were living unsuitably far away, sometimes in other countries. Some patients who were recorded as having had absent tendon reflexes while in hospital had normal jerks by the time they were seen again. These factors naturally limited the number of cases available. No attempt was made to assess the incidence of abnormalities of the tendon jerks. One patient with sporadic cortical cerebellar atrophy of late onset was also examined.

The case histories are given in the appendix.

Methods:

Stimulation of the medial popliteal nerve and recording of the ankle jerk.

Results:

The patients who had had cerebellar tumours had absent ankle jerks on the homolateral side, the left in two instances and the right in the third. The patient with cerebellar atrophy had bilaterally absent ankle jerks.

The "H" wave was present in every case.

Discussion:

I will first of all comment on a few points which are relevant to the old controversy between van Gehuchten (1907) and Philippe and Lejonne (1904) on the significance of changes in the posterior roots. None of my cases showed any sensory disturbances and all had normal superficial reflexes. In this way, they resembled van Gehuchten's case (1907).

This lack of sensory disturbances is certainly an argument in his favour, though not a very strong one since it does not rule out selective changes in the posterior roots. If the changes described by Philippe and Lejonne (1904) were caused as they suggested by a transmission of the high intracranial pressure, the operative factors would presumably be traction on the nerve roots subsequent to displacement and ischaemia. These are known to be more apt to affect the larger nerve fibres (Lewis and Pochin 1938), that is those involved in the tendon jerk.

Another point is that the reflex changes persisted a long time after the relief of the raised intracranial pressure and occured in a case of cerebellar atrophy (J.C.) where the intracranial pressure was certainly not raised.

More conclusive evidence against ascribing much significance to posterior root changes is that in these cases the "H" wave was retained. This is contrary to my findings in patients with known lesions of the posterior nerve roots.

Van Gehuchten's suggestion that there was an interruption of excitatory pathways other than the corticospinal is much more convincing to us today.

Rossi (1927) was probably the first to realise the importance of the motor innervation of muscle spindles in the regulation of muscle tone. In a paper on the effect of cerebellar lesions on posture he made the following almost prophetic statement: "centri piu elevati non debbano occuparsi, per cosi dire, di inviare impulsi alle celluli motorie che innervano direttamente il musculo ma che sia forse sufficiente una lora azione sugli elementi contrattili degli organi di recezione".

This when taken together with the more recent work on supraspinal control of the gamma motorneurones provides us with an explanation for the areflexia occasionally associated with cerebellar lesions.

Granit and Kaada (1952) in a paper already referred to, studied the effect of stimulation of various parts of the cerebellum. Most of the experiments were carried out in cats under chloralose-dial anaesthesia but some unanaesthetised decerebrate preparations were used. The afferent discharge from muscle spindles was recorded from single fibres in the posterior roots and the gamma efferent discharge recorded directly from the anterior roots. The afferent discharge arising from the muscle spindles of the gastrocnemius muscle increased during stimulation of the hemispheral part of the anterior lobe and decreased markedly and stopped altogether during stimulation of the vermal part. Confirmation that this effect was mediated by a cerebellar influence on the gamma motorneurones was provided by the direct recording of gamma discharge from the anterior nerve roots. Eldred (1955) has reported similar results during stimulation of the dentate and interposite cerebellar nuclei and the brachium conjunctivum.

Ablation and cooling experiments (Granit et al 1955) have produced results which fit in with the picture of cerebellar control of gamma discharge suggested by the earlier stimulation experiments. Clear-cut and reversible results were obtained by cooling the anterior lobe of the cerebellum in the decerebrate cat.

Cooling silenced the spindle discharge and rewarming of the cerebellum restored the original picture. Similar, though not quite so clear cut effects resulted from surgical ablation of the anterior lobe or its functional inactivation by the Pollock and Davis (1923) technique. Granit et al (op. cit.) were careful to emphasize that paralysis of the gamma-system sometimes did not occur following ablation and that it was never complete following the anaemic decerebration of Pollock and Davis. They suggested that the different extent of the cerebellar lesion might explain this discrepancy and some of their data actually hint that cerebellar cortex destruction alone might not account for the results. Dow and Moruzzi (1958) believe that cooling may be more effective because it involves the sudden disappearance, without irritation, of cerebellar function.

The only relevant human experiments are those of Struppler and Schenck (1958). They found that in patients with cerebellar lesions the 'silent period' (Merton 1951) does not occur. Merton (1951) showed that when a twitch contraction is superimposed on a steadily contracting muscle, the electromyogram shows a period of silence of approximately 30 m.secs following the twitch. He interpreted this as being due to sudden 'unloading' of the spindles during muscle shortening.

If we suppose that in patients with cerebellar lesions there is a paralysis of the gamma-system and that voluntary contraction is mediated entirely by the alpha-pathway (Granit 1955) the absence of a 'silent period' comes as no surprise.

My own experiments viewed in the light of the observations reported above, provide further evidence for this supposition. The loss of reflexes in cerebellar disease could be interpreted as being the results of either a loss of excitation of gamma-motorneurones or as an increase in inhibition. The former appears more likely in view of the destructive nature of the lesions, the fact that the changes persisted for so long after operation and that in one case they were produced by an atrophic process.

Unfortunately, these cases do not add anything to the problems of localising the part of the cerebellum responsible for control of the gamma-system. The tumours were too large to allow us to draw any conclusion from their site and although the sporadic type of late cortical cerebellar atrophy affects the anterior lobe. predominantly,it is not restricted to that region. Indeed the possibility of involvement of the medullary reticular formation cannot be excluded.

In summary then, I have presented evidence suggesting that the areflexia seen in some patients with cerebellar lesions is caused by gamma-paralysis.

EPILEPSY

Introduction:

In the course of this study, it was realised that a number of epileptic patients, some inpatients, others outpatients, had absent tendon jerks. These fell roughly into two groups:

1) Those whose fits were well-controlled on large doses of anticonvulsant drugs but who were showing signs of overdosage.
2) Those who had very frequent fits and were bordering on status epilepticus and patients examined within 6 hours of having had a fit. The patients in the second group were taking only small or moderate doses of anticonvulsant drugs or were receiving no treatment at all. None showed signs of overdosage.

The evidence reported in previous chapters had suggested that a lesion in the spinal cord or brain stem could abolish the ankle jerks by disrupting the pathways concerned with supraspinal excitation of the gamma motor-neurones. In view of the current theories that generalised epilepsy may be associated with neural discharges originating in the reticular formation of the brain stem (Penfield and Jasper, 1954; Gastaut, 1954) it seemed possible that during the phase of "exhaustion" following a fit, there might be a disturbance of

supraspinal facilitation which might account for the absence of tendon reflexes. It was also thought possible that anticonvulsants, as well as damping down the activity of the ascending reticular activating mechanism might also interfere with the descending facilitatory impulses and thus produce a depression of tendon reflexes.

A. The Effect of some Anticonvulsants on the Ankle Jerk.

The clinical picture of phenytoin toxicity is well known. It was described by Meritt and Putnam (1939) very early after the introduction of the drug. It usually consists of a "cerebellar" syndrome with ataxia, inco-ordination and nystagmus. The state of the ankle jerks is seldom mentioned in the early descriptions but Roger and Soulayrol (1959) noted a marked depression of all tendon reflexes.

The neurological picture of primidone toxicity is very similar (Goodman and Gilman 1955).

Material: 1) The first 4 subjects were epileptic patients showing side effects due to large doses of anticonvulsants. In all these cases, the main drug in use was either phenytoin or primidone. All the patients had marked nystagmus, ataxia and inco-ordination. The tendon reflexes were very sluggish and the ankle jerks were absent. None had had any fit in the week preceding the experiment.

2) One normal subject was given large doses of phenytoin by mouth (400 mg four times daily) and another was given primidone (1 G four times daily) until each developed ataxia with nystagmus and absent ankle jerks. Because the ataxia so produced took a few days to develop and 4 - 5 days to disappear, this method of giving the drugs was considered impracticable and further experiments were carried out with phenytoin injected intravenously (there is no preparation of primidone for intravenous injection).

3) The injection of phenytoin was given intravenously in doses of 250 mgm to 10 normal subjects, to whom the nature of the experiment had been explained. This usually produced nystagmus and a depression of tendon reflexes within half an hour of the injection. The advantage of this method was that the effect was transient and any inco-ordination had usually disappeared two hours after the injection.

4) One of the 10 subjects (a boy aged 13 years) was given a smaller dose (150 mg) of phenytoin intravenously.

5) Three other normal subjects were given 500 mgm of phenytoin intravenously.

6) A control group of 6 patients were given an intravenous injection of 5 mls of normal saline.

Methods:

1) Recording of the ankle jerk.

2) Stimulation of the medial popliteal nerve (as described in the section on methods).

Results:

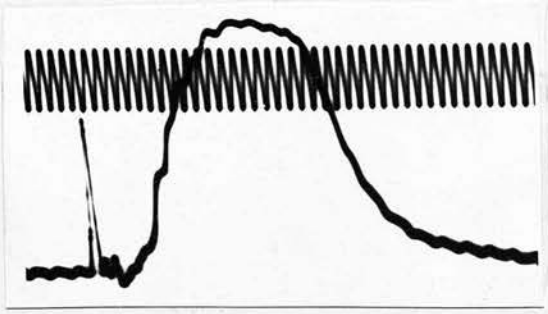
1) The 4 epileptic subjects and the 2 normals who had been given large doses of anti-convulsants will be considered first. They all showed similar results. The ankle jerk was abolished but the "H" wave was retained. In the normal subjects given anticonvulsants orally the responses were variable: the ankle jerks were usually absent but sometimes just obtainable; the "H" wave, however, was always present.
When the dose of anticonvulsants was reduced or stopped altogether, co-ordination improved, nystagmus disappeared and the tendon jerks returned. Neither the amplitude nor the threshold of the "H" wave was altered.

2) The 10 normal subjects given phenytoin 250 mg intravenously all showed a marked diminution of the amplitude of the ankle jerk within half an hour following the injection. The jerk, however, was never completely abolished since I did not exceed the dose recommended by the manufacturers.

The measured change in the amplitude of the record obtained for each subject under standard conditions is given in table 2 . Analysis shows that the amplitude changes are highly significant ($P < 0.001$). The "H" wave remained unchanged in threshold, maximum amplitude, and in amplitude at fixed stimulus current (Fig. 13).

Table 3 shows that with one exception there was no significant change in the threshold of the "H" wave. No test of significance was applied to the readings for the amplitude of the "H" wave as there was no measurable fluctuation in these, and the readings after phenytoin were exactly the same as those before phenytoin. The result in case 9 was an exception. There was a significant rise in the threshold of the "H" wave (Before injection: Mean: 5.74; S.D.: 0.09; After injection: Mean: 6.18; S.D.: 0.05; $P = < 0.001$). This subject also showed a slight diminution in amplitude of the "H" wave at fixed stimulus current (Before: Mean: 4.0; S.D.: 0.05; After: Mean: 3.82; S.D.: 0.05; $P = < 0.001$), and a diminution in the maximum amplitude of the "H" wave (Before: Mean: 6.2; S.D.: 0.05; After: Mean: 5.74; S.D.: 0.05; $P = < 0.001$) with no change in any of the parameters of the "H" wave.

3) To confirm this dose effect, I gave a larger dose of i.v. phenytoin to 3 adult subjects. This produced a rise in threshold and a fall in amplitude of the "H" wave and the usual depression of the ankle jerk (Tables 4 and 5).



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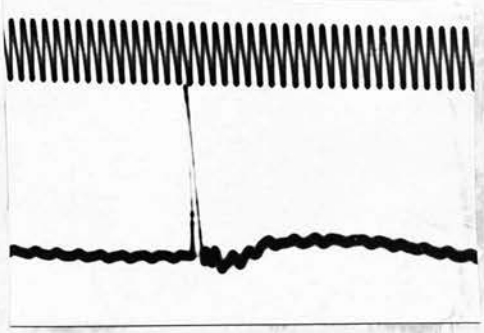

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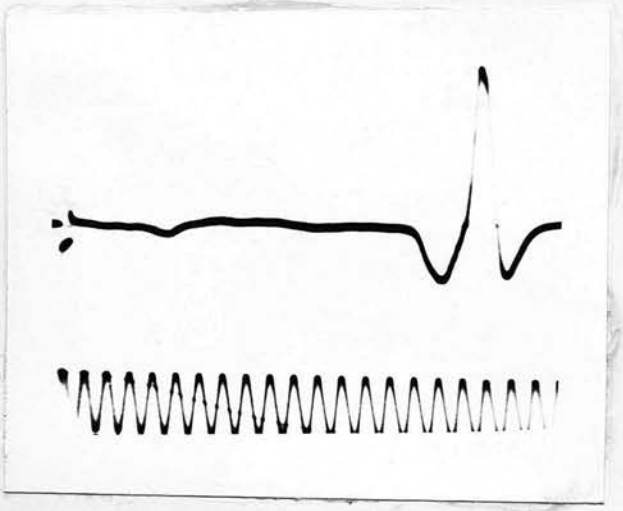

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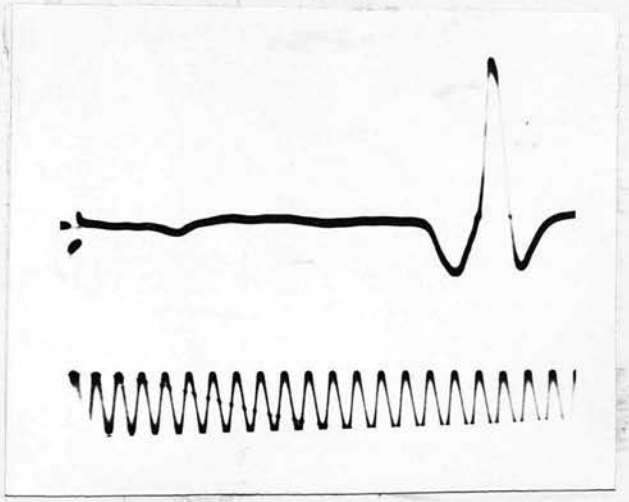


d.

Fig. 13

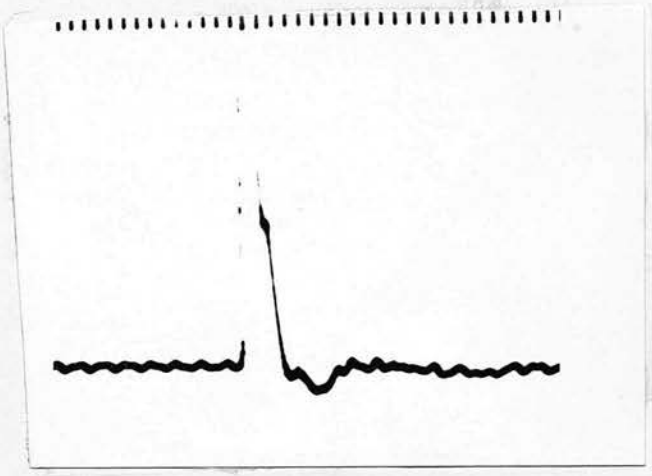
Fig. 13 - Normal subject.

a) The ankle jerk before injection of phenytoin.

b) The ankle jerk after injection of 250 mgm of phenytoin intravenously. Time 100 c/s.

c) The "H" wave before injection of phenytoin.

d) The "H" wave after injection of phenytoin.



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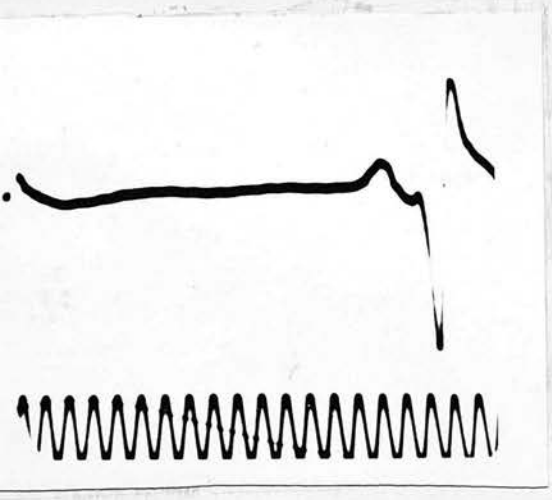

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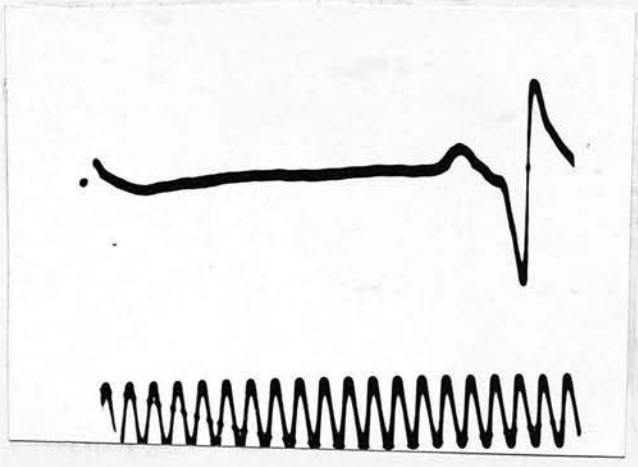


c.

Fig. 14

Fig. 14 - Normal subject.

a) Showing a severe depression of the ankle jerk after injection of 500 mg of phenytoin intravenously. Time 100 c/s.

b) The "H" wave before the injection. Time 500 c/s.

c) The "H" wave after the injection. Time 500 c/s.

4) The control group of 6 subjects given 5 mls of saline i.v. showed no change in either the "H" wave or the ankle jerk.

No change in amplitude, threshold or latency of the "M" wave was observed in any of the experiments, indicating that the peripheral neuromuscular apparatus was not appreciably modified by the drugs in the doses used.

Table 2

Ten normal subjects: Amplitude (cms) of the ankle jerk before and after 250 mgm of phenytoin i.v.

	Amplitude before		Amplitude after		
Subject	Mean:	S.D.	Mean:	S.D.	P *
1	6.40	0.15	2.66	0.13	< 0.001
2	4.94	0.05	3.46	0.05	< 0.001
3	5.56	0.12	1.88	0.09	< 0.001
4	6.74	0.05	5.28	0.05	< 0.001
5	4.60	0.10	2.06	0.05	< 0.001
6	6.06	0.09	3.42	0.05	< 0.001
7	3.42	0.09	1.76	0.05	< 0.001
8	5.30	0.07	1.86	0.09	< 0.001
9	6.78	0.05	1.60	0.07	< 0.001
10	4.56	0.22	2.08	0.10	< 0.001

* As measured on the wave recorded on photographic paper.

Table 3

Ten normal subjects: threshold (m Amps) of the "H" wave before and after 250 mgm phenytoin i.v.

	Threshold before		Threshold after		
Subject	Mean	S.D.	Mean	S.D.	P *
1	10.26	0.05	10.24	0.05	> 0.5
2	12.18	0.18	12.18	0.09	1.0
3	7.62	0.09	7.56	0.15	> 0.4
4	5.70	0.15	5.64	0.15	> 0.5
5	13.86	0.34	13.6	0.37	> 0.9
6	8.58	0.05	8.56	0.05	> 0.5
7	9.86	0.09	9.9	0.05	> 0.6
8	6.22	0.09	6.22	0.09	1.0
9	5.74	0.09	6.18	0.05	< 0.001
10	10.44	0.09	10.48	0.05	> 0.4

* P was determined by means of Fisher's "T" test.

Table 4

Three normal adults: threshold (m Amps) of "H" wave before and after 500 mgm phenytoin l.v.

Subject	Before		After		
	Mean	S.D.	Mean	S.D.	P *
A	9.76	0.05	13.38	0.17	< 0.001
B	5.66	0.15	10.36	0.26	< 0.001
C	5.84	0.11	12.24	0.16	< 0.001

Table 5

Three normal adults: amplitude of "H" wave (cms) before and after 500 mgm of phenytoin l.v.

Subject	Before		After		
	Mean	S.D.	Mean	S.D.	P *
A	6.12	0.05	2.0	0.11	< 0.001
B	5.3	0.07	3.6	0.07	< 0.001
C	5.8	0.05	2.0	0.12	< 0.001

DISCUSSION:

The results of the tests on the subjects receiving oral phenytoin or primidone suggest at first that these anticonvulsants can depress and sometimes altogether abolish the ankle jerk without apparently affecting the reflex arc proximal to the stretch receptors or at any rate without interrupting it altogether. The later experiments with large doses of phenytoin i.v. make it clear that this simple picture has to be modified slightly.

It would seem that the effect depends on dosage. The larger doses have effects which are qualitively as well as quantitatively different from the smaller doses. They will be discussed separately.

If one considers once again Granit's (1955) diagram of the innervation of skeletal muscle (chapter on Friedreich's ataxia) it is clear that a block in any of a number of sites could explain the differential effect seen with smaller doses of anticonvulsants.

1) In the afferent fibres between the muscle spindles and the point of stimulation in the medial popliteal nerve. This seems highly unlikely since there was certainly no block proximal to the point of stimulation and there is no reason to believe that there is any difference between these fibres above and below the knee.

Nevertheless, this possibility cannot be entirely excluded at this stage in view of the demonstration by Morrell et al (1958) that phenytoin increased the threshold and decreased the spike amplitude in peripheral nerve fibres. However, the doses used by these workers were considerably higher (700 - 1050 mg) than the ones I have used. Final exclusion of this point will require a careful study of sensory nerve action potentials in the distal part of the medial popliteal nerve.

2) In the muscle spindles themselves, this is also possibility which cannot be entirely ruled out at this stage. The effects of phenytoin on the body have been studied extensively. Its sites of action include peripheral nerve (Toman 1949, 1952; Morrell et al 1958), spinal cord (Stille 1955, Esplin 1957), cerebellum (Utterback et al 1957, Hoffmann 1958), diencephalon (Gangloff and Mounier 1955) and many others but I have found no reference to direct effect of muscle spindles. This remains a possibility.

3) Somewhere along the "gamma pathway", that is, in the gamma motorneurones or gamma efferent fibres themselves or alternatively as I have described before, in the supraspinal excitatory pathways which control the gamma motorneurones (Granit and Kaada 1952, Granit 1955).

Gangloff and Mounier (1955) have attempted to determine the site of action of a number of anticonvulsants. They have shown that phenytoin considerably raises the threshold for stimulation of the reticular formation and shortens the after discharge. On the other hand, in the doses given, the effects on the cerebral cortex and "rhinencephalon" were negligible. It has also been shown by Utterback et al (1957) and by Hoffmann (1958) that in phenytoin intoxication there occurs a widespread parenchymatous degeneration of the cerebellum with disappearance of Purkinje cells. These findings are not surprising to the clinician familiar with the striking resemblance between phenytoin intoxication and cerebellar disturbances. When these findings are considered together with the knowledge we have of the intimate relationship between the cerebellum and the gamma systems (Granit et al 1955) and the fact that spindle discharge is very effectively controlled by the mesencephalic reticular formation (Granit and Kaada 1952) it seems reasonable to interpret the effects I have described in terms of an interference of the supraspinal facilitatory influences which normally play on the gamma-motorneurones.

The effect of the larger doses of phenytoin can clearly not be interpreted solely in these terms. All the parameters of the "H" wave showed changes pointing to an interference in the reflex arc proximal to the point of stimulation of such a type as to restrict the number of

motorneurones recruited reflexly.

Two possibilities may be considered:-

1) The changes in the parameters of the "H" wave could be a reflection of the rise in threshold and decreased spike amplitude in alpha fibres described by Morrell et al (1958). One objection to this has already been raised - the dose used by these workers was appreciably higher than even the largest doses used in my experiments. The absence of change in threshold amplitude or timing of the "M" wave rules out this possibility.

2) The changes could be due to an effect of phenytoin on the spinal cord. Esplin (1957) has carried out an extensive study of the effects of phenytoin on synaptic transmission in the cat spinal cord in an attempt to obtain clues concerning the mechanisms by which anticonvulsants act to reduce seizure activity. He has shown that maximal isolated monosynaptic responses are reduced although the reduction is even more marked in polysynaptic potentials. The drug did not affect direct facilitation or inhibition on the alpha motorneurone. It deepened presynaptic depression following transmission of an impulse and "enhanced transmission failure during repetitive stimulation". It also caused a striking reduction in post-tetanic potentiation. Although the doses were large (30 mg/ Kg) he claims that they were in the non-toxic range for cats.

The effects of the drug on repetitive activity does not concern us here but its effects on the isolated monosynaptic response are obviously relevant to this discussion. This synaptic depression would certainly explain the changes in the "H" wave which I have observed following the administration of high doses of phenytoin.

In summary then, it is suggested that the first effect of phenytoin (and possibly of primidone) on the ankle jerk is due to spindle depression consequent on interference with supraspinal facilitation of the gamma-motorneurones. When higher doses are given there is a further effect due to the action of the drug on synaptic transmission in the spinal cord.

B. The Effect of frequent or recent fits on the Ankle Jerk.

Both Hughlings Jackson and Gowers took an interest in the condition of the tendon jerks and plantar responses following an epileptic fit. At that time the "tendon phenomenon" was just becoming known and accepted, but all interest was concentrated on the knee jerk. When the ankle was mentioned it was usually only to draw attention to the presence or absence of ankle clonus. The ankle jerk itself was seldom mentioned.

Hughlings Jackson (1881) was probably the first to describe the presence of ankle clonus and excessively brisk knee-jerks following an epileptic fit. Beevor (1883) carried out a more detailed study of the knee jerk in 70 cases of generalised epilepsy. He found that when seen within 1 - 2 minutes of a fit, 38 of these patients showed increased knee jerks, 26 diminished or absent knee jerks, and in the remaining 6, the jerk was normal. Unfortunately, the ankle jerk (as distinct from ankle clonus) is not mentioned.

Gowers (1881 b) in his book on epilepsy says 'A severe attack leaves the muscles flabby and apparently atonic, and during this condition, in some cases, when the fit has been very severe, the knee-jerk ("patellar tendon-reflex") cannot be obtained'. He pointed out that in most cases the knee-jerk was in fact increased and there was ankle clonus, but he differentiated between three conditions of these phenomena: "After slight attacks there may be no change in the myotatic contractions, after fits of greater severity there may be foot-clonus and increased knee jerks, and after very severe fits, there may be for a short time a loss of the knee-jerk, which is followed by a stage of excess".

Kinnier Wilson in his text book (1955 b) referring to the post-ictal period states 'as regards cutaneous and deep reflexes, during the terminal period of complete atony and powerlessness, the knee jerk is at times abolished. More generally, the negative phase fails to develop, exaggeration being observed together with ankle clonus and extensor plantar responses'.

It was felt that the method of evoking a reflex which by-passed the muscle stretch receptors might supply additional information about the areflexic phase to which this study was limited.

Material:

Six patients with generalised epilepsy were studied. These patients had had very frequent 'grand mal' attacks and most had had a fit in the six hours preceding the test. Two of them had fits just as they were about to be tested and the experiment was started within a few minutes of cessation of the convulsive movements.

All six had absent ankle jerks but no obvious weakness. The plantar responses were either absent, equivocal or frankly extensor.

Methods:

1) Recording of the ankle jerk

2) Stimulation of the medial popliteal nerve

Results:

No ankle jerk could be recorded from any of the subjects but the "H" wave was present in every case. The patients were tested later at varying intervals after the control of their fits when the ankle jerks were found to have returned but no obvious change was detectable in the "H" wave.

Although no great effort was made to time the duration of the areflexia, in every case it was found to be of the order of several hours or even days and certainly longer than the 'few minutes' suggested by both Beevor (op.cit.) and Gowers (op. cit.).

The return of the tendon jerk was not accompanied by any obvious hyper-reflexia.

Discussion:

These findings suggest that the areflexia has a similar mechanism to that which has already been invoked in the section on the effect of phenytoin, namely a temporary loss of the facilitatory impulses which normally impinge on the gamma-motorneurones.

If we accept the current theories which suggest that generalised epilepsy originates from massive discharge in the reticular formation and postulate that during this discharge both the ascending and the descending activating mechanisms are involved, the changes in the reflex arc become more intelligible. Following a severe fit or a rapid succession of fits, cells in the reticular formation concerned with facilitation of the gamma-motorneurones may enter into a prolonged refractory state such as presumably affects the 'alpha pathway' during post-ictal hemiplegia or Todd's paralysis. Since none of my cases showed any obvious weakness when examined, the presumed 'exhaustion' of the 'gamma pathway' would seem to outlast that of the 'alpha pathway'.

If the suggested process of exhaustion affects inhibitory fibres as well as facilitatory ones, it is easy to see how a variation in the balance between the two could produce either areflexia or hyper-reflexia.

Both Beevor (op.cit.) and Gowers (op. cit.) insisted that the depression of the knee-jerk after a fit was very brief and probably of the order of 1 - 2 minutes. Although this may be true of some cases it was certainly not so in those I have described where the depression of the jerks lasted several hours or usually several days.

The cases I have described also differ from those in the classical descriptions in the lack of a subsequent hyporeflexia. It may of course be that I did not test the patients sufficiently quickly after the fit and that there was an early areflexia followed by a hyperflexia and then by a second areflexia, and that I only examined in this last stage. However, two of the subjects were certainly tested within a minute of the cessation of the fit. In order to carry out a detailed study of the sequence of events it would be probably be necessary to induce fits by means of drugs or photic stimulation or to study the tendon reflexes of patients receiving electro-convulsive therapy (E.C.T.). This was not attempted since this work was concerned only with the areflexic phase, but further studies of this problem are planned.

PARKINSONISM

Introduction:

In the general introduction to this thesis, I pointed out that abnormalities of the central nervous system are still being interpreted in ways which take no account of recent neurophysiological discoveries concerning the afferent control of the muscle spindles. This criticism does not apply in the field of spasticity and rigidity where numerous workers (Hassler 1956; Schaltenbrand and Hufschmidt 1957; Schaltenbrand and Hufschmidt 1959; Barraquer -Borbas 1957, 1958; Asai and Hufschmidt 1958; Rushworth 1960; Jung and Hassler 1960) have presented theories which incorporate these new ideas. This fresh approach has been particularly fruitful in the study of Parkinsonism where it has provided the basis for a number of interesting if sometimes conflicting theories.

While not proposing to assess fully the relative merit of these different theories of the pathophysiology of Parkinsonism, I will deal with some of them only in so far as they concern organisation at the spinal cord level. For this reason, I will not discuss some important contributions to the study of Parkinsonism such as that of Denny-Brown (1960).

Within the limits of this discussion the main theories can best be divided into two groups. The first group covers the work of the German school (Hassler op. cit.; Schaltenbrand op. cit.; Schaltenbrand and Hufschmidt op. cit. Asai and Hufschmidt op. cit.; Jung and Hassler op. cit.). The clearest and most elaborately worked out exposition representing this group is that of Jung and Hassler (op. cit.).

These workers make a clear distinction between the two components of the stretch reflex. They differentiate between the slow, polysynaptic stretch reflex for which the receptor organ is probably the myotube or 'flower-spray' endings of the muscle spindles and mediated via 'tonic' motorneurones (Eccles 1957 a, 1957 b) in theanterior horn of the spinal cord and the rapid monosynaptic stretch reflex or 'tendon jerk' which probably involves the annulospiral endings and 'phasic' motorneurones (Eccles 1957 a, 1957 b). They stress the point made by von Holst (1951) that in Parkinsonian rigidity as distinct from spasticity, there is a loss of the automatic control of muscle length ('servo-mechanism of length') which is normally dependent on annulospiral endings and that the muscle becomes regulated entirely by the automatic control of its tension ('servo-mechanism of tension') through the myotube endings and the Golgi tendon organs.

This is suggested by the fact that in Parkinsonian rigidity, the muscle adapts to any imposed change by lengthening or shortening but maintains a constant resistance to the passive movement imposing the change.

Jung and Hassler (op. cit.) remind us that the interneurones of the spinal cord are controlled by synchronising and desynchronising influences (Magoun and Rhines 1946, 1947; Niemer and Magoun 1947) and that these facilitate or inhibit the slow, polysynaptic reflexes. The inhibitory impulses seem to originate at least partly in the strionigral system and to travel along nigro-reticulo-spinal pathways. They suggest that there is a deficiency of this desynchronising and inhibitory effect and that the descending pallido-reticular influences originating in the external pallidum predominate, exerting their synchronising effect and enhancing the polysynaptic reflexes.

As far as the monosynaptic ('phasic') stretch reflex is concerned, they point out that it is not enhanced, and suggest that on the contrary there is probably a disturbance of the activity of the central supraspinal mechanisms for facilitation of the gamma-motorneurones. They back this view with the results of experiments on reinforcement (Hassler 1956) and show that it is consistent with von Holst's (1951) remarks on the loss of automatic control of muscle length.

The second group of theories includes those of Barraquer-Borbas (op. cit.) and Rushworth (op. cit.). These two theories are very similar in the role which they attribute to the stretch reflex. Neither is as elaborately worked out as that of Jung and Hassler.

Rushworth (op. cit.) stresses the reflex basis of muscular rigidity but does not make a clear distinction between the behaviour of the polysynaptic and the monosynaptic reflexes in Parkinsonism. His experiments seem to have been concerned entirely with the polysynaptic reflexes and he shows that these are enhanced. On the basis of experiments with procaine he tentatively suggests that 'in spasticity, rigidity and dystonia, the gamma-motor-neurones are overactive, thus increasing the sensitivity of the annulospiral endings of the muscle spindles to stretch'.

Although I do not propose to examine these theories in detail, my study of some abnormalities of the monosynaptic reflex in a group of patients with Parkinsonism appears relevant.

Material:

Five cases of Parkinsonism found on clinical examination to have absent ankle jerks were tested. One of these was of the post encephalitic type, the others were of idiopathic type. Short case histories are given in the appendix. All showed slight or moderate rigidity and tremor.

It was intended to test patients before and after a stereotaxic operation on the pallidum or thalamus but only one of them (R.S.) was treated surgically during the period of this study. In this patient the neurosurgeon made a right pallido-capsular lesion.

Methods:

1) Recording of the ankle jerk

2) Stimulation of the medial popliteal nerve

Results:

No ankle jerk could be recorded from these patients but in every case the "H" wave was easily obtainable.

In case R.S. there was a return of the ankle jerk and a diminution in rigidity on the contralateral side following operation.

Discussion:

The tendon reflexes in Parkinsonism are usually described as being normal or slightly depressed. Russell Brain (1955) says "Parkinsonism does not involve any essential changes in the reflexes, though rigidity may render the tendon-jerks difficult to elicit and reduced in amplitude". The mechanism for the depression which is implied in this statement seems to be that a strong and simultaneous contraction of a set of antagonistic muscles (flexor and extensors of the ankle in this case) such as may occur in severe rigidity may make the tendo-Achilles so taut that the blow of a tendon-hammer will hardly produce any stretching at all. This mechanism can be seen in a patient who fails to relax and can be produced voluntarily by strong and simultaneous contraction of both sets of muscles. In this case the reflex is 'interrupted' at its periphery, or rather, never set in motion at all. An alternative interpretation could be that the muscles may contract maximally in rigidity and any superimposed contraction becomes impossible. Whichever of these two alternatives is chosen, Brain's (op. cit.) statement implies some sort of direct correlation between the rigidity and the state of the reflexes.

In fact, the patients I have tested showed only mild or moderate rigidity and yet had no ankle jerks, whereas cases with severe rigidity without loss of tendon reflexes are quite common. There does not in fact appear to be any direct correlation between the severity of the rigidity and the state of the tendon-jerks.

At this stage, a few words about the different types of rigidity may be apt. The experiments of Pollock and Davis (1923, 1930, 1931) have shown that following ligation of both carotid and basilar arteries in the cat, a type of decerebrate rigidity is produced which is affected only slightly by posterior root section. This led to the suspicion that two distinct forms of decerebrate rigidity might exist. This suspicion was further reinforced by the work of Eldred et al (1953). These workers compared gamma motorneurone activity in the ordinary decerebrate cat to that in the Pollock and Davis animal. By using the discharge of single spindle afferents, they have shown that the ordinary decerebrate cat has marked gamma motorneurone activity whereas the Pollock and Davis animal has not. These two forms have been named gamma rigidity and alpha rigidity respectively. Matthews and Rushworth (1957 a, 1957 b, 1958) showed that dilute procaine applied to a mixed nerve abolished the rigidity of the muscle it supplied in the gamma cat but did not at first affect that of the alpha cat.

An attempt has been made to extrapolate from these observations on decerebrate animals to human spastic and rigid states. Thus, Rushworth (1960) uses the diminution of previously hyperactive polysynaptic stretch reflexes following procaine infiltration in cases of Parkinsonism to support his contention that in these cases there is hyperactivity of the gamma motorneurones. He also quotes the reduction of rigidity following posterior root section (Förster 1911, 1913 a, 1913 b; Pollock and Davis 1930) to confirm this view. Several objections can be raised against his argument.

The first concerns the interpretation of the results of posterior root section and procaine infiltration. Both these techniques,by abolishing or reducing the bombardment of the anterior horn cells by afferent impulses, will diminish the overall excitation of these cells and restrict the 'subliminal fringe'. This will occur whether the excitability of the alpha-motorneurones has previously been raised by direct supraspinal excitation or by an increase in impulses from stretch receptors. That is, whether the rigidity is of alpha or gamma type. Admittedly, one would expect the gamma type to be more susceptible to these methods but I do not think that a simple reduction of rigidity after procaine or, worse still, a simple reduction in amplitude and duration of the myotatic reflex as recorded by a concentric needle electrode, can be used as evidence.for saying that Parkinsonian rigidity

is of gamma type. Until one can give a more quantitative estimate of rigidity and demonstrate a greater reduction in one than in another, all interpretations based on the effect of procaine infiltration on rigidity are fraught with difficulties.

The second objection to Rushworth's hypothesis is one of fact. He claims that "the classical decerebrate rigidity of animals, spasticity in man, and parkinsonian rigidity are all due to increased tonic stretch reflexes and are reduced or abolished if the appropriate dorsal roots are cut". However, careful examination of the relevant paper of Pollock and Davis (1930) shows that the relaxation of Parkinsonian rigidity following a posterior rhizotomy of C4 to T4 did not persist. In fact, within 11 days of operation the patients had developed apparently fixed 'contractures'. These were, in fact, manifestations of hypertonicity and not true contractures since they disappeared during sleep. This rigidity following complete deafferentation of the affected muscles suggests that descending excitatory influences impinging directly on the alpha-motorneurones must have contributed to the rigidity. In other words, there was an 'alpha' element in the rigidity.

A further objection to Barraquer-Borbas (op. cit.) and Rushworth's interpretations is evident when one considers the state of the tendon jerks in cases of

Parkinsonism. If, as they suggest, the 'gamma-system' as a whole is hyperactive in Parkinsonism one would expect patients to have brisk tendon jerks. This is not the case. In fact, apart from those post-encephalitic cases with signs of 'pyramidal tract' involvement, Parkinsonian patients have reflexes which are "difficult to elicit and reduced in amplitude" (Brain 1955) and as we have seen, they may be absent altogether. This difficulty arises from the failure to differentiate clearly between the state of the slow, polysynaptic component of the reflex and that of the rapid, monosynaptic component.

Jung and Hassler (1960) make this distinction quite clearly and the picture which they draw of the pathophysiology of Parkinsonism is much more consistent with the clinical picture of the disease and is in keeping with my observations. They write "to a large extent, the increase in muscle tone in rigor is due to an enhancement of the myotatic reflexes, that is of the tonic component of the stretch reflexes, whereas there is no enhancement of the phasic (monosynaptic) component stretch reflexes". They go further and state that "there is probably in them (Parkinsonian patients) a deficient activity of the central supranuclear mechanisms for gamma innervation".

They base this conclusion partly on the assumed loss of the 'servo-mechanism of length' and partly on the behaviour of the tendon jerks of Parkinsonian patients during the Jendrassik manoeuvre.

Sommer (1940) and Hoffmann (1951) showed that during this manoeuvre there was no change in the amplitude of the "H" wave although the ankle jerk became larger. This has been confirmed recently by Buller and Dornhorst (1957) who concluded that the Jendrassik manoeuvre must potentiate the tendon jerk by increasing the discharge down the gamma motorneurones and thus raising the sensitivity of the annulospiral endings. Hassler (1956) has shown that this method of enhancing reflexes has little or no effect in Parkinsonian patients and used this to support his contention that in this disease there is a 'deficient activity of central supranuclear mechanisms for gamma innervation'. While agreeing with his conclusion I do not think that it is a justifiable one to draw simply from the failure of reinforcement by the Jendrassik manoeuvre. The phenomenon might equally be explained by the hypothesis that the gamma motorneurones are already firing at maximal frequency and that the jerk is already 'reinforced' maximally. However, I have already given reasons for believing that this second interpretation is not the correct one.

It therefore seems reasonable to accept Jung and Hassler's (1960) view regarding the loss of gammacontrol of the monosynaptic reflex rather than Barraquer-Borbas (op. cit.) and Rushworth's (op. cit.) suggestions.

This view is also supported by an old observation of Byrnes' (1926) which has been largely ignored. This worker described histological changes in muscle spindles and their nerves in long-standing cases of paralysis agitans. It is possible that the disturbance of the spindles is a purely functional one at first, but that morphological changes eventually develop. This would explain the fact that both medical and surgical treatment are much more effective in the early cases, before irreversible anatomical changes have occurred. In case R.S. the reversibility of the reflex abnormality in an early case was demonstrated.

Hassler's theory also fits with the suggestion of Merton (1953) that during controlled movements impulses in the'gamma system'precede those in the'alpha system', the former having a kind of 'starter function'. It is precisely this 'starter function' that is deficient in Parkinsonism and this deficiency probably accounts for their slowness in initiating controlled movements although they are quite capable of performing a sudden 'instinctive' movement such as catching a ball when it is thrown at them. This latter movement is probably mediated by impulses travelling directly down the spinal cord to the alpha motorneurones (Merton 1953).

The apparently paradoxical situation under which the polysynaptic reflexes are enhanced while the monosynaptic ones are depressed, still requires comment. Schaltenbrand and Hufschmidt (1957) have found that in Parkinsonism the central excitation of the gamma fibres is supressed only for phasic, proprioceptive reflexes, and not for the tonic. polysynaptic ones. This difference between the behaviour of the two types of reflexes is not surprising when it is borne in mind that Granit and Holmgren (1955) discovered two different central pathways conveying impulses from the mid-brain to the gamma-motorneurones. One is a fast conducting, crossed pathway in the lateral funiculus and the other a slow probably multisynaptic pathway which was not interrupted by lesions short of almost complete cord section. It is possible that only the fast conducting central pathway which Jung and Hassler (1960) identify as the nigro-reticulo spinal system, is deficient in the cases of Parkinsonism I have described.

The evidence presented here therefore seems to support the Jung and Hassler (1960) hypothesis, postulating a deficiency of gamma innervation in Parkinsonism.

POLYMYOSITIS

The validity of the concept of 'polymyositis' has been cogently argued by Walton and Adams (1958) and is now generally accepted. This porte-manteau term is a convenient one at present because of the poor understanding we have of the causation and pathogenesis of acquired diseases of muscle. It is clear that the term covers a number of conditions and may later need to be abandoned as these begin to emerge as definite entities.

The state of the tendon jerks in these conditions is rather puzzling. They are sometimes surprisingly brisk, sometimes normal, and often absent (Rosenthal and Hoffmann 1923; Walton and Adams 1958). Occasionally, the state of the reflexes bears no relation to the severity of muscle involvement, being very brisk in very weak muscles and sluggish or even absent in muscles which are only slightly affected. In these cases it is very difficult to attribute the loss of reflexes to direct involvement of extrafusal muscle fibres.

In the course of this study, two such cases came to my attention and they were selected for further examination.

Material:

Both cases were women with histological confirmation of the clinical diagnosis of polymyositis. The case histories are given in the appendix.

Methods:

1) Recording of the ankle jerks
2) Stimulation of the medial popliteal nerve
3) Motor nerve conduction studies in the lateral popliteal nerve
4) Needle electromyography: this was performed with a concentric needle electrode of Adrian and Bronk type. The technique is now well-established and will not be described any further since it played only a very minor part in the investigation.

Results:

1) No ankle jerk was recordable from any of the cases
2) The "H" wave was present in both cases
3) The motor nerve conduction velocity was within natural limits. The results are tabulated below.

Subject:	Conduction Delay with Stimulation At Knee (m. secs)	Conduction Distance (cms)	Delay with Stimulation at ankle (m.secs)	Conduction Distance (cms)	Velocity (m/sec)
M.J.	10	40	4	8	53
C.T.	9	41	3.5	8.5	59

4) Needle electromyography:

M.J. (left calf). There was an excess of insertion activity but no spontaneous activity at rest. A normal number of motor units were recruited on maximal voluntary contraction but many units were small and very brief ('myopathic' in type) and there was a large number of highly polyphasic units.

Other muscles showed similar changes and in addition, 'fibrillation'potentials were recorded from the first dorsal interosseus muscle at rest.

C.T. (left calf). Excessive insertion activity was recorded and there was very marked fibrillation. The units recruited on voluntary contraction were small, brief and polyphasic.

Discussion:

The results of the experiments involving stimulation of the medial popliteal nerve appeared somewhat surprising at first, but their similarity to those obtained in other unrelated conditions can be explained.

If one reconsiders the different sites at which lesions may be expected to produce loss of the ankle jerk with retention of the "H" wave, it is clear that two of the possibilities which were considered unlikely in Friedreich's ataxia and phenytoin intoxication, must be seriously considered in polymyositis. They are:

1) The muscle spindles themselves
2) The peripheral branches of the afferent nerves

Little attention has been paid to the state of muscle spindles in diseases of muscle, structural alteration in cross-sections of the intrafusal muscle fibres being rather difficult to interpret. It is generally held that they are spared in the majority of muscle diseases (Adams et al 1953; Greenfield et al 1957). However, Greenfield et al (1957) have described definite fibrotic changes in the muscle spindles of a small group of cases including a case of acute dermatomyositis, and Bosanquet et al (1960) state that in polymyositis "muscle spindles may be involved in the general degeneration".

Such abnormalities may be quite common since no systematic pathological examination of the spindles has been carried out in polymyositis. Such involvement of the muscle spindles would be expected to interfere with the stretch reflex without affecting the reflex arc proximal to the receptors.

The second possibility which might explain the results is an interruption of the reflex arc in the afferent nerve fibres below the point of stimulation in the medial popliteal nerve. Although there were no clinical signs indicative of peripheral neuropathy in the cases I have studied, involvement of the terminal intramuscular nerve fibres remains a distinct possibility.

The term 'neuromyositis' was coined by Senator (1893) to described a group of cases of dermatomyositis with involvement of peripheral nerves, and although the concept of neuromyositis is rejected by many (Walton and Adams 1958) there is now considerable evidence, clinical, pathological and electromyographic , suggesting that peripheral nerves, especially the terminal intramuscular nerves can be affected in polymyositis.

Gowers (1899) described the association of polyneuritis and polymyositis in one of his cases, and Marinésco (1910) ascribed the muscular and nervous lesions to a common agent.

Kinney and Maher (1940) have described a demyelination in peripheral nerve trunks of a fatal case of polymyositis, and van Bogaert and Rademecker (1954) have reported cases of polymyositis showing endoneurial cellular infiltrations and loss of myelin in terminal intramuscular nerves. Greenfield et al (1957) found endoneurial fibrosis in the case of dermatomyositis mentioned above. On the other hand Coers (1953, 1954) using an intravital staining technique with methylene blue demonstrated the integrity of the terminal intramuscular axons (at any rate, the motor ones) in spite of marked muscular degeneration and cellular infiltration in two cases of polymyositis. However, these observations of Coers cannot be set against those mentioned above since it is suggested that only a proportion of cases show peripheral nerve involvement. In any case, Coers (1954) himself has described an unusually complex arborisation of terminal nerve fibres in polymyositis, and Walton and Adams (1958) who are firm opponents of the concept of neuromyositis found pathological changes in the peripheral nerves in one of their cases.

Unfortunately, the pathological reports on my cases were unhelpful as the sections were not stained specifically for terminal nerve fibres or for muscle spindles. No spindles were seen in the sections but since this is not unusual in normal cases, no conclusions can be drawn from this negative observation.

Electromyographic and chronaximetric evidence of a neuropathic lesion has also frequently been reported. van Bogaert and Rademecker (1954) mention a case showing such chronaximetric changes, Simpson (1954) has obtained curves like those found in denervation in patients with unequivocal polymyositis, and Richardson (1956) found spontaneous duration curve indicative of neuropathy in 8 out of the 20 cases he examined. Bauwens (1956) obtained strength-duration curves pointing to partial denervation and found fibrillation at rest. He applied to these cases the term 'terminal neuronitis' but now believes that they were cases of polymyositis or 'neuromyositis'.

That such changes may have occurred in the cases I have included in this study, is suggested by the electromyographic finding of fibrillation at rest. If the process involved the afferent fibres as well as the efferent, it provides another possible explanation for the reflex changes. Since only the terminal fibres would be affected, the reflex arc proximal to the point of stimulation in the medial popliteal nerve would be intact and the "H" wave therefore obtainable. On the other hand, the lesion would interrupt impulses produced by stretching of the muscle spindles and therefore abolish the ankle jerk.

In summary then, a lesion either in the muscle spindles themselves or in the terminal afferent fibres supplying them, or a combination of both, would provide a plausible explanation for those cases of polymyositis where the depression of the tendon jerks is out of proportion to the weakness of the muscles subserving them.

INTRATHECAL PHENOL

Since Maher's original paper in 1956 a number of publications have described the use of intrathecal injections of phenol for a variety of conditions. The main indications for its use have been intractable pain (Maher 1955, 1957, 1960; Brown 1958) and severe spasticity with troublesome flexor spasms (Matthews 1959; Kelly and Gautier Smith 1959).

The effect of phenol on nerve conduction following its application to the spinal roots of cats has been studied by Nathan et al (1958); Nathan and Sears (1960); Iggo and Walsh (1959 and 1960). These workers obtained largely similar results. They concluded that small fibres were far more susceptible to the action of the drug than the large fibres.

Brown (1958) in his paper on the relief of pain noted in passing that "superficial and deep reflexes vanish and never return. While resting, muscle tone is permanently and considerably reduced, voluntary power is unaffected".

In the period over which this study was carried out, a number of patients were treated with this substance in the hope of relieving their painful flexor spasms. All showed absent ankle jerks immediately following the injection. Four such patients were selected for further study.

Material:

The four patients were suffering from disseminated sclerosis and painful flexor spasms. They were studied before and after the intrathecal injection of varying quantities and concentrations of phenol in glycerol.

The choice of dose and timing of the injections was dictated entirely by the therapeutic requirements of the case concerned. The injections were carried out in the ward by the clinical staff of the unit where this work was done. My experiments had naturally to fit in as well as possible with the therapeutic programme.

Short case histories are given here rather than in the appendix as some of the clinical observations are directly relevant to the discussion.

Miss J. McE.: This patient was fifty-four. She had a four year history of disseminated sclerosis. She had suffered from severe and painful flexor spasms in the right leg for two years and more recently these had affected the left leg as well.

On examination she was found to be slightly dysarthric. There was a horizontal nystagmus which was more marked when the eyes were deviated to the right. The right arm and leg were spastic, weak and inco-ordinate.

Miss J.McE. (contd.)

The tendon jerks were all very brisk and there was ill-sustained clonus at both ankles. The plantar responses were extensor and the abdominal reflexes absent. Vibration sense was absent on the right side from the level of the iliac crest downwards, Otherwise sensation was normal.

Lumbar puncture (L.P.) revealed clear cerebrospinal fluid (C.S.F.) under normal pressure. The protein content was 30 mg/100mls, the colloidal gold curve 444321000 and the Wassermann reaction (W.R.) and Kahn tests were negative.

On January 24, 1961, L.P. was performed at the lumbar (L.) 2 - 3 interspace with the patient on her right side and 1.4 mls of 5% phenol in glycerol were injected.

On January 26, 1961 the injection was repeated as it was considered that the release of spasm in the hip flexors was insufficient. The needle was introduced at the L 2 - 3 interspace with the patient lying on her right side and the foot of the bed raised. 1.5 mls of 5% phenol were injected.

Mrs C.C. This 51 year old patient had an eight year history of cervical spondylosis and disseminated sclerosis. The spondylosis had been dealt with by a postero-lateral decompression but she had had persistent and painful flexor and adductor spasms in the left leg.

On examination she was found to have mild dysarthria, horizontal nystagmus and a brisk jaw jerk. There was a marked increase in tone in the right arm and in both legs which were also weak. The tendon jerks were very brisk, the left more so than the right. The plantar responses were extensor and the abdominal reflexes absent. Co-ordination was poor but sensation was normal. Frequent left-sided flexor and adductor spasms were observed.

Lumbar puncture revealed clear C.S.F. under normal pressure. There was a partial block in flexion. The protein content was 40 mg/100 mls and the colloidal gold curve 3333221100. The W.R. and Kahn tests were negative.

Intrathecal injections of 1.5 m.s of 5% phenol were given on January 25, 1961 and February 3, 1961 at the L 2 - 3 interspace with the patient on her left side and the foot of the bed raised.

Mr G.M.: This 65 year old male gave a 20 years history of weakness and stiffness of both legs. More recently he had developed urgency and frequency of micturition, slight slurring of speech and parasthesiae in the fingers of both hands. He suffered from painful flexor spasms of the right leg.

He had nystagmus on looking to the right and a slight left ptosis. The upper limbs were normal apart from showing slight intention tremor. Tone was greatly increased in the right leg, less so in the left.

Mr G.M. (contd.)

There was a global weakness on both sides most marked in the hip flexors, hamstrings and tibialis anterior. The knee and ankle jerks were brisk on both sides, the plantar responses were extensor and the abdominal reflexes absent. There was a loss of proprioception below the hip on the right side and in the toes on the left. Vibration sense was lost at the right ankle. Other modalities of sensation were normal.

Lumbar puncture revealed clear C.S.F. under normal pressure and with normal consitutents.

On April 12, 1960, lumbar puncture was performed at the L 3 - 4 interspace while the patient lay on his right side. 1.5 mls of 2% phenol in glycerol were injected.

Mr D.P. This was a forty-eight year old patient with a typical history of disseminated sclerosis stretching back over a period of 20 years.

Both optic discs were pale. There was bilateral intention tremor, more marked on the right side, and a spastic paraparesis. The tendon jerks were very brisk and there was well sustained clonus at the right ankle. The plantar responses were extensor and the abdominal reflexes absent. Vibration sense was lost below the iliac crests on both sides.

Mr D.P. (contd.)

Repeated injections of phenol in varying quantities and concentrations were given at different levels over a period of several months.

2/11/59: L.P. was carried out at the L 3 - 4 interspace with the patient on his right side. 0.9 mls of 5% phenol were injected.

18/1/60: L.P. at L 3 - 4 with the patient on his left side. 1 ml. of 2% phenol was injected.

4/5/60: L.P. at L 3 - 4 with the patient on his right side. 2 mls of 2% phenol were given.

12/5/60: L.P. at L 3 - 4 with the patient on his right side. 2 mls of 5% phenol were injected.

7/7/60: L.P. at L5 - S1 with the patient on his left side. 1.5 mls of 5% phenol were injected.

Methods:

The methods applied in studying these patients have already been outlined. The ankle jerk was recorded in the usual way and the medial poplitel nerve stimulated in such a way as to produce an "H" wave recordable over the calf muscles.

In addition, a careful neurological examination was carried out both before and at frequent intervals after the injection of phenol. Particular attention was paid to the state of the reflexes and any changes in sensation were noted.

Results:

Miss J. McE. The ankle jerk was of large amplitude and the "H" wave easy to elicit. Its threshold and amplitude are given in tables 6 and 7 . Following the first injection, there was a marked reduction in tone at the right knee and ankle but the hip flexors remained hypertonic. The right knee and ankle jerks diminished in amplitude. Thirty minutes later there was an impairment of superficial sensation in the S. dermatomal distribution. Power was significantly affected. The right knee jerk was still diminished in amplitude and the right ankle jerk was absent. Later that day the sensory loss receded but the ankle jerk remained absent.

Miss J.McE. (contd.)

The "H" wave, however, was present and there was a significant change in its parameters (see tables 6 and 7). These changes were still present two days later when the injection was repeated in order to relieve the spasm in the hip flexors. Soon after this second injection, the patient experienced a warm sensation over the anterior aspect of the right thigh and a sensory loss developed in the right T9-S1 dermatomal distribution. There was also some impairment of proprioception. The leg became flaccid and the knee jerk disappeared. There also developed a very severe paresis and obvious fasciculation in a number of muscles.

No further tests were carried out on this subject as there were now such widespread and diverse deficits on both the motor and the sensory side that no useful conclusions could be drawn about the relative importance of the lesions in the different parts of the reflex arc.

Mrs C.C. The ankle jerk was of wide amplitude and there was sustained clonus. The "H" wave was recorded as usual. Following the injection on January 25, 1961, there was a diminution in tone in the hip and a transient loss of both knee and ankle jerks on the left side, associated with anaesthesia in the L 1 - 3 territory. At a time when the ankle jerk was absent, the "H" wave was easily elicited and was unchanged in threshold and amplitude.

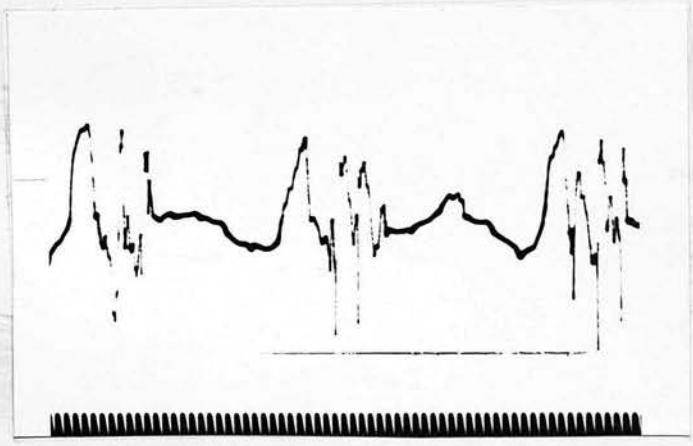


Fig. 15

Fig. 15 - C.C. - a patient suffering from disseminated sclerosis. Electromyographic recording obtained 3 days after an intrathecal injection of phenol and demonstrating ankle at a time when the patient showed a marked flaccidity of the lower limbs. Time 100 c/s.

Mrs C.C. (contd.)

Three days later, the limb was still flaccid but clonus had returned to the left ankle. The anaesthesia was now restricted to the L 2 distribution.

A week after the first injection the spasms had returned and sensation was normal. The injection was repeated and was followed by a release of spasm and and a transient loss of the left tendon jerks with anaesthesia in the L 2 distribution. On the following day the jerks had returned, there was still ankle clonus, sensation was normal but tone was still much reduced.

No significant paresis developed after either of the injections but fasciculation was observed on a number of occasions in several lower limb muscles including those of the calf.

Mr G.M. Both the ankle jerks and "H" waves were extremely easy to elicit before the phenol injection. After the injection there was an immediate loss in sensation on the right side from L 1 downwards and the right knee and ankle jerks could not be elicited. Simultaneously, there was a marked reduction in tone. On the following day, the impairment of sensation was less severe and limited to the region below the L 3 level. The jerks were still absent. The "H" wave was present but there was a rise in its threshold and a fall in its amplitude. These changes were significant ($P < 0.001$).

Mr G.M. (contd.)

Two days later the knee jerks had returned and the sensory disturbance had receded to what it was before the injection, i.e. a proprioceptive impairment only. The ankle jerk, however, was still absent but the "H" wave had regained its previous threshold and amplitude.

The ankle jerk remained absent until his discharge about five months after the injection. When he was seen again about a year after the administration of phenol the ankle jerk had returned although it was difficult to elicit.

Mr D.P. Following the first injection he developed an anaesthesia at first over the S1 distribution. When the foot of the bed was tilted up, there followed a complete anaesthesia from the L 2 level downwards and a flaccidity of the right leg with abolition of the tendon jerks. The little movement which existed before was retained. On the following day, sensation had returned to normal but the jerks were absent. The "H" wave was present and unaltered in threshold and amplitude.

The second injection was carried out about six weeks later in order to relieve the left sided symptons. It resulted in a depression of sensation over the L 2 - 5 dermatomes and a diminution in tone at the hip and knee with abolition of the knee and ankle jerks.

Mr D.P. (contd.)

Two days later the sensory loss had receded, but the tendon jerks were absent. The parameters of the "H" wave were unchanged.

During the three month period following this, the ankle jerks remained absent and he had two further administrations of phenol. However, later there was a tendency for left sided spasticity to recur and the ankle jerks returned.

A further injection was undertaken in order to relieve spasticity at the left ankle. This was achieved. There was a transient anaesthesia in the S1 distribution and again an abolition of the ankle jerk.

This patient also was noticed to have frequent fasciculation in a number of lower limb muscles and this persisted for months.

Discussion:

Iggo and Walsh (1960) have demonstrated the selective action of phenol in the cat. They determined the relative sensitivity of various categories of fibres to this substance by applying it directly to the nerve rootlets. Using natural stimuli, they found that proprioceptive fibres were more resistant than cutaneous fibres. When using electrical stimuli, they found that the small myelinated fibres were more susceptible than the larger ones and in particular that the gamma-efferent fibres were very sensitive. Nathan and Sears (1960) have obtained substantially similar results.

My results in human subjects seem to confirm this. Thus, following the injection of phenol, the ankle jerk was abolished at a time when there was no sensory loss at all or certainly none in the root distribution involved (L 5 - S 1) and no increase in paresis. The "H" wave was still easily obtainable implying as I have already argued, that the reflex arc proximal to the knee was largely intact.

The rise in threshold and diminution in amplitude of the "H" wave in some of the instances requires some explanation. This sort of change has been reported by Landau et al (1960) following intrathecal injection of procaine in normal subjects. It may be as Landau suggests a manifestation of the drop in excitability of the anterior horn cells consequent on the abolition of tonic impulses from the muscle spindles, or it may be due to a partial

block of the muscle afferents in the posterior roots. My own experiment (reported earlier) showed no change in the parameters of the "H" wave in normal subjects following procaine infiltration of the medial popliteal nerve, implying that in the healthy resting subject tonic discharges from muscle spindles do not contribute very much to the total excitability of the anterior horn cells. This contribution may be more important in the spastic patient but we have no evidence that this is so when such a patient is at rest. The fact that in some of the cases there was no change in the "H" wave when a marked spasticity had been relieved, would seem to argue against this interpretation. Since these changes in the "H" wave were seen only in cases where there was, or had recently been, a sensory loss involving the sacral segments it appears likely that there was at least some involvement on the afferent side of the reflex arc.

Two other points deserve brief comment. One concerns the duration of the changes in the tendon relfexes. Brown (1958) reported them as being permanent but this was not so in the case I have described above. There was on the contrary a tendency for the tendon jerks to return after a period of time varying from about a day or two to several months.

Presumably the duration of the effect depends on a number of factors, for instance the dose and concentration of phenol and the vehicle used to dissolve it, the proximity of the needle to nerve roots and individual variations of local anatomy.

The other point relates to the finding of ankle clonus in the presence of flaccidity in C.C. This has been described in the past. As early as 1907 van Gehuchten wrote: "Ces modifications dans le tonus normal des muscles, qu'elles se manifestent par l'hypertonie, par l'hypotonie ou par l'atonie sont indépendentes des modifications qui peuvent survenir dans l'etat des reflexes tendineux. L'exageration des reflexes tendineux pouvant aller jusqu'au clonus du pied et au clonus de la rotule peut exister avec une hypotonie musculaire".

This interesting dissociation between the two components of the stretch reflex in C.C. indicates that the phenol may have had some effect on motor fibres, especially or possibly solely on the 'tonic' alpha motor fibres (Eccles et al 1958) while leaving the 'phasic' ones intact. Indeed, the fact that there was fasciculation in various muscles makes it very likely that at least alpha-motor fibres were affected.

In summary, I have presented evidence suggesting that the effect of intrathecal phenol on the tendon reflexes is mainly due to its blocking of the gamma-motor fibres in the anterior root, but also, in some cases, to an effect on the muscle afferents in the posterior roots and possibly to an involvement on the motor side.

Table 6

The amplitude (cms) of the "H" wave before and after phenol.

Subject:	Amplitude (cms) before		Amplitude (cms) after		P *
	Mean:	S.D.	Mean:	S.D.	
J. McE.	4.22	0.09	3.76	0.09	< 0.001
G.M.	5.06	0.112	4.72	0.05	< 0.001

Table 7

The threshold (mA) of the "H" wave before and after phenol.

Subject:	Threshold (mA) before		Threshold (mA) after		P *
	Mean:	S.D.	Mean:	S.D.	
J. McE.	10.45	0.05	9.5	0.10	< 0.001
G.M.	7.5	0.11	6.45	0.10	< 0.001

* Values for P were obtained by means of Fisher's T-test

THE HOLMES-ADIE SYNDROME

This eponymous title was first applied by Bramwell (1936) to a syndrome including dilatation of the pupil, apparent loss of reaction to light, slow constriction and relaxation in response to near and distant vision, impaired or delayed accommodation, and loss of some of the tendon jerks.

Holmes published his account in 1931 and Adie (1932) was probably the first to distinguish the condition clearly from neurosyphilis. However, the syndrome was certainly known at least 100 years before. Riddell (1937) attributed the first description of a case to James Ware, and English surgeon who published an account in 1813. In Germany, Strasburger, Saenger and Nonne independently described the clinical manifestations in 1902.

In France, the condition is often known as the Weill-Reys syndrome after the two ophthalmologists who gave the first account in the French Literature in 1926.

A great deal has been written about the possible pathogenesis of the pupillary abnormality and at least six different sites have been suggested for the presumed lesion. The literature on this subject has been admirably reviewed by Russell (1957) in reporting work done in this unit.

On the other hand, comparatively little attention has been paid to the absence of tendon reflexes although this was noted in the classical descriptions of Holmes (1931) and Adie (1932).

The knee and ankle jerks are most commonly affected, but Graveson (1949) reported loss of upper limb jerks in eight of his sixteen patients and total areflexia in three cases. Russell (1958) found loss of some of the upper limb jerks in seven of his fifteen cases and loss of all tendon reflexes in two.

The cause of this areflexia remains unknown. This is not surprising since the benign nature of the condition makes it extremely difficult to obtain material for pathological examination. As far as I know, no one has ever examined the spinal cord, nerve roots and peripheral nerves of a case of Holmes-Adie syndrome.

Careful clinical examination is usually unrevealing. Kyrieleis (1951) stated that he found no disturbance of muscle tone. Bolsi (1952), however, found slight alterations in deep sensation and a variety of deformities of the spinal column. A striking feature in these patients is the lack of any postural or proprioceptive disturbance as assessed by clinical testing. Hufschmidt and Schaltenbrand (1959) have shown that the polysynaptic stretch reflex is intact in patients with Holmes-Adie syndrome and this appears sufficient to allow them to regulate their posture and movements accurately.

Among the few writers who have tried to explain the loss of tendon reflexes, Bolsi (op.cit.) attributed them to the bony abnormalities which he found, the effective agent being presumably pressure or traction on the posterior roots,and Domzal (1955) suggested that both the areflexia and the pupillary disorder could be explained by a mesencephalic lesion.

As has been pointed out already, the monosynaptic reflex can be affected by a lesion in any of the following sites:

1) The stretch receptors
2) The peripheral nerves (afferent fibres)
3) The posterior nerve roots
4) The synapses in the spinal cord
5) The anterior horn cells (alpha motorneurones)
6) The anterior horn cells (gamma-motorneurones)
7) The anterior nerve roots (alpha-efferent fibres)
8) The anterior nerve roots (gamma-efferent fibres)
9) The peripheral nerves (alpha-efferent fibres)
10) The peripheral nerves (gamma-efferent fibres)
11) The motor-end plates
12) The extrafusal muscle fibres
13) The supraspinal facilitatory pathways

This work will attempt to show which of these sites is the most likely.

Material:

Nine cases of Holmes-Adie syndrome were tested. Most of them have already been reported by Russell (1957, 1958). Table 8 shows the age and sex distribution and the particular tendon reflexes lost. It incidentally contradicts the assertions of Adie (1932) and Kennedy et al (1938) that loss of upper limb reflexes is uncommon and gives further support to Graveson (1949) and Russell (1957, 1958) who both insisted that it was not.

Methods:

1) Motor nerve conduction studies on the lateral popliteal nerve.

2) Recording ofreflexes and "H" waves.

Table 8

Nine cases of Holmes-Adie syndrome showing age and sex distribution and tendon jerks lost.

Case	M. or F.	Age	Biceps		Triceps		Supinator		Knee		Ankle	
			R	L	R	L	R	L	R	L	R	L
M.C.	F	27	X	X	X	X	X	X	–	–	–	–
M.C.	F.	40	–	–	–	–	–	–	–	–	–	–
M.S.	F.	62	–	–	–	–	–	–	–	–	–	–
L.S.	F	42	–	–	–	–	–	–	–	–	–	–
M.H.	F	32	X	–	–	–	–	–	–	–	–	–
W.L.	M	35	X	X	X	X	–	–	–	–	–	–
F.M.	F	63	–	–	–	–	–	–	–	–	–	–
I.R.	F	51	–	–	–	–	–	–	–	–	–	–
A.Y.	F	11	–	–	–	–	–	–	–	–	–	–

Table 9

Motor nerve conduction in the lateral popliteal nerve of 9 cases with Holmes-Adie syndrome.

Case	Velocity in metres/sec.
M.Ca.	52
M. Co.	58.3
M.S.	47.5
L.S.	46.8
M.H.	55.5
W.L.	60
F.M.	43.6
I.R.	55.7
A.Y.	61.1

Results:

1) Motor nerve conduction was within normal limits in every case (see table 9).

2) The "H" wave was absent in every case tested in spite of the fact that the stimulus was increased to the maximum tolerable level. The "M" wave was easily obtainable.

Discussion:

I think these results supply a partial answer to the question raised in the introduction to this section.

It is clear that disease or dysfunction of the stretch receptors cannot account for the results since these suggest that the lesion was proximal to the point of stimulation of the medial popliteal nerve. A lesion in the stretch receptors would also have to be very selective, affecting only those involved in the monosynaptic reflex and sparing those involved in the polysynaptic reflex since the latter has been shown to be intact (Hufschmidt and Schaltenbrand 1959).

These considerations rule out site (1). The lesion is also clearly not in the peripheral nerve distal to the point of stimulation.

Sites 5), 7), 11) and 12) are also ruled out since one would expect a patient with a lesion on the motor side of the reflex arc to show considerable weakness before having a loss of tendon jerks. We can also exclude 9) for the same reason and because of the normal motor nerve conduction which was described above.

Let us now consider suggestion 13) - the supraspinal facilitatory pathways. This is the mechanism implied by Domzal (1955) when he suggested that both the areflexia and the pupillary disorder could be explained by a lesion in the brain stem. It is presumably the same mechanism as that which I have described in the section on Friedreich's ataxia.

A number of writers have favoured the brain stem as being the region most likely to be involved in the causation of the ocular abnormalities. McKinney and Frocht (1940) have suggested that the lesion responsible for the myotonic pupil is in the pre-tectal part of the mid-brain, and Kennedy et al (1938), Barré et al (1950) and Bonamour (1952) have mentioned the 'diencephalon'. Such sites as these might explain the occasional association of the Holmes-Adie syndrome with narcolepsy (De Morsier and Franceschetti 1953) grand mal, 'syncopal convulsions and other diencephalic disorders' (Hetzel and Niedermeyer 1959), cerebellar tumour (Thiébaut et al 1954) and its reported causation by disseminated sclerosis (Holmes 1931) and encephalitis (Gayer-Morgan and Symonds (1927).

However, an association has also been reported with a variety of other conditions including pernicious anaemia (Petit and Delmond 1936), Raynaud's disease (Heersema and Moersch 1939), diphtheria (Marx 1952, Bonamour 1952), 'mental disease' (Petit and Delmond 1936; Heuberger 1954) and a great variety of other disorders. Although it is possible that some of these conditions, e.g. pernicious anaemia, might have been associated with brain stem lesions, it is equally, if not more likely, that the Holmes-Adie syndrome was a chance accompaniment, since this disorder is probably reasonably common.

In any case, even if a brain stem lesion is present in Holmes-Adie syndrome, the mechanism suggested by Domzal (op. cit.) for the areflexia is probably not the correct one. A lesion in the supraspinal pathways would not be expected to interfere with the reflex arc in such a way as to abolish the "H" wave. The fact that the "H" wave was unobtainable probably excludes his suggestion. It also excludes the possibility of a lesion in the gamma-motorneurones or gamma-efferent fibres 6), 8) and 10), since these would abolish the tendon jerk but not the "H" wave (cf. chapter on Friedreich's ataxia).

The only remaining sites where a lesion might be considered are:- the peripheral nerve proximal to the point of stimulation (2), the posterior nerve roots (3), and the synapses in the spinal cord (4). A lesion in any of these could explain the loss of both "H" waves and tendon jerks. It is difficult to push the argument very much further but a few tentative remarks can be made about the probability of a dysfunction at one of these sites.

Motor nerve conduction appeared to be normal and sensation was unimpaired so that any factor operating on the peripheral nerves or nerve roots would have to be selective, destroying the sensory fibres concerned with the stretch reflex and sparing the motor fibres and all the other sensory fibres. Since Hufschmidt and Schaltenbrand (1959) have shown that in the Holmes-Adie syndrome in contrast with tabes dorsalis, the polysynaptic reflex arc is intact, the disease process would have to pick out only those afferent fibres concerned with the monosynaptic stretch reflex. Such a selectivity though not impossible appears rather unlikely.

Such a dissociation is more easily conceived of as operating in the spinal cord itself. If a large proportion of the synapses were affected by this disturbance the impulses involved in the monosynaptic reflex might be blocked whereas those subserving the polysynaptic reflex would have a greater chance of

of 'finding' a healthy alternative chain of synapses.

Vojir (1958) examined cases of the Holmes-Adie syndrome who had preserved their knee jerks and found that although the contraction phase of the reflex was normal, the relaxation phase was slow and prolonged. Struck by the analogy between this and the myotonic pupil he suggested that this pointed to a single lesion in the diencephalon, explaining both. However, it is equally likely and more in keeping with the results, that there may be several lesions of a similar nature, probably biochemical, coexisting at different levels in the nervous system.

Although no final answer can be given, the evidence seems to favour the theory that some sort of synaptic pathology lies behind the areflexia of the Holmes-Adie syndrome. This would explain the lack of any sensory or proprioceptive disturbance and the loss of both the "H" wave and the tendon jerks.

CONCLUSIONS

This study has shown:

1) that in tabes dorsalis, polyneuritis, the Holmes-Adie syndrome, some cases of motor neurone disease, muscular dystrophy and in 'mixed' cases of Friedreich's ataxia, both the ankle jerk (including the "T" wave) and the "H" wave may be absent.

2) that in 'pure' Friedreich's ataxia, in cerebellar diseases, in the post-ictal state and in some cases of Parkinsonism and of polymyositis, the "H" wave may be retained although the tendon jerk is lost.

3) that in motor neurone disease with severe weakness there was a loss of the "M" wave as well.

4) that phenytoin given in moderate doses depresses the jerk without affecting the "H" wave, although if larger doses are given both show a diminution in amplitude.

5) that intrathecal phenol may affect only the tendon jerk, but that if it has caused a lasting disturbance of sensation it will affect the "H" wave as well.

These results, together with those of nerve conduction studies and the evidence of other workers reviewed in this thesis, may be used to draw certain tentative conclusions about abnormalities of the reflex arc.

Theoretically, a lesion in any of a number of sites could affect the tendon jerks. These sites have been outlined previously. They are repeated below:

1) The stretch receptors
2) The peripheral nerve (afferent fibres)
3) The posterior nerve roots
4) The synapses in the spinal cord
5) The anterior horn cells (alpha-motorneurones)
6) The anterior horn cells (gamma-motorneurones)
7) The anterior nerve roots (alpha-efferent fibres)
8) The anterior nerve roots (gamma efferent fibres)
9) The peripheral nerves (alpha efferent fibres)
10) The peripheral nerves (gamma efferent fibres)
11) The motor end-plates
12) The extrafusal muscle fibres
13) The supraspinal facilitatory pathways

It has been pointed out how only sites (2), (3), (5), (7), (9) and (12) are usually taken into consideration.

This investigation set out to study the possibility that lesions in the other regions might cause abnormalities of the tendon reflexes.

It has been suggested that:

(a) In 'pure' forms of Friedreich's ataxia, in those rare cases of disseminated sclerosis with loss of tendon reflexes and in diseases of the cerebellum, the abnormality can be accounted for by an interruption or withdrawal of facilitating impulses to the gamma-motorneurones, leaving the afferent side of the reflex arc intact, but that in the 'mixed' forms of Friedreich's ataxia (Roussy-Levy syndrome), the lesions in the peripheral nerves are sufficient to explain the areflexia.

(b) Phenytoin given in moderate doses may produce this effect on the gamma motorneurones but given in larger doses it may depress synaptic transmission in the spinal cord.

(c) A similar disturbance of the motor innervation of muscle spindles may also occur in Parkinsonism where there may be a depression of the monosynaptic stretch reflex with a simultaneous enhancement of the polysynaptic stretch reflexes.

(d) Phenol injected intrathecally blocks the gamma-efferent fibres but in those patients who show lasting sensory disturbances there is an additional effect on the afferent fibres.

(e) In some cases of polymyositis with loss of tendon reflexes in the absence of marked weakness there may be a lesion in the muscle spindles themselves or in the terminal intramuscular afferent nerve fibres, although this will require histological confirmation.

(f) In tabes dorsalis and polyneuritis the lesions in the posterior nerve roots or in the peripheral nerves are sufficient to account for the areflexia.

(g) In the Holmes-Adie syndrome, the disturbance is probably one of synaptic transmission in the spinal cord.

(h) In motor neurone disease and muscular dystrophy the lesion is, not surprisingly, on the motor side.

It can be tentatively concluded that lesions at (1), (4), (8), (10) and (13) can be responsible for abnormalities of the tendon reflexes. Lesions in the gamma-motorneurones themselves (6) have not been encountered. Site 11 - the motor end-plates - also remains a distinct possibility but although fatiguability of the tendon-jerk is sometimes seen in myasthenic patients and is occasionally severe enough to cause abolition of the ankle jerk (Brune 1961), no such case was seen during the course of this investigation.

It should be stressed that in the majority of cases, absence of tendon reflexes is accounted for in 'orthodox' terms. These include the countless numbers of cases of polyneuritis and tabes seen by neurologists everywhere. The other causes are comparatively rare.

Suggestions for further investigations:

In this study I have attempted to show that previously obscure abnormalities of the tendon reflexes can be interpreted by taking into consideration the information that neurophysiologists have given us about the motor innervation of muscle spindles.

I have concerned myself almost entirely with the monosynaptic reflex. Our understanding of spinal reflex abnormalities in man could be greatly extended by a similar study of the polysynaptic reflexes. There are individuals, for example, cases of Holmes-Adie syndrome who show very gross abnormalities of the monosynaptic reflex arc and yet have a normal posture and gait. This apparent contradiction of the assumed importance of the two-neurone stretch reflex in the maintenance of posture has always been puzzling. It is very likely that in these subjects co-ordination is almost entirely dependent on polysynaptic reflexes.

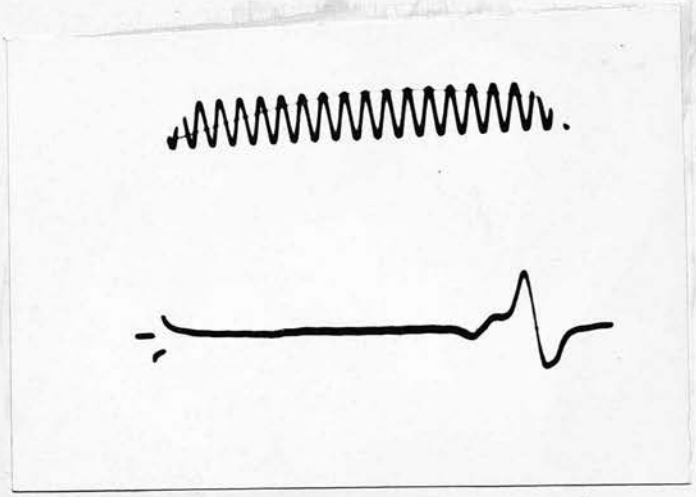
The technique of medial popliteal stimulation could be adapted for the study of these reflexes. For instance, Magladery et al (1950 a) have already been able to record "late waves" which appeared some time after the "H" wave. They believe these to be reflex in origin. If this can be confirmed we have here a further tool for the investigation of the areflexias.

Other workers, for instance, Hufschmidt and Schaltenbrand (1959) have been using the so-called 'silent period' to study tendon jerk abnormalities. At the present stage it is difficult to see how their work will produce any useful results. These workers have failed to standardise their technique and seem to draw firm conclusions from the flimsiest of experimental material. Even if it is assumed that proper standardisation is possible, there are also very great difficulties in interpreting the results since the length of the 'silent period' depends on at least four interrelated factors:

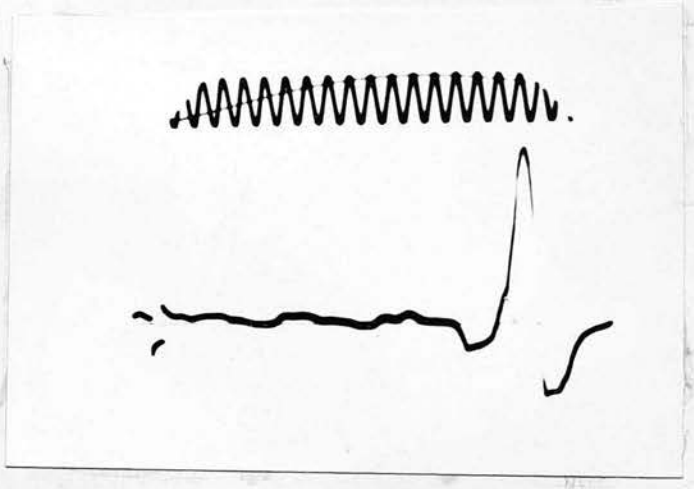
1) The refractory period of simultaneously discharged motorneurones
2) The inhibition of the anterior horn cells through the recurrent axon collaterals of Renshaw
3) The 'unloading' of muscle spindles
4) Autogenetic inhibition from tension receptors in muscle and tendon.

Equally difficult to interpret are the results of tests using the Jendrassik manoeuvre to reinforce the tendon jerk (Hassler 1956; Buller and Dornhorst 1957). Although it is generally true that during this manoeuvre the tendon jerk increases in amplitude while the "H" wave remains unchanged, this only applies provided that the leg muscles are kept absolutely relaxed during the procedure. If this precaution is not taken the "H" wave also becomes larger (fig. 16). Some workers do not appear to have appreciated this. The diagram shown in Hassler (1956) and Jung and Hassler's (1960) papers show, incidentally, a considerable amount of background activity recorded from the calf muscles. This suggests that their subject was contracting his leg muscles during the Jendrassik manoeuvre and therefore invalidates their conclusions. In any case, failure to reinforce may be interpreted as being due either to a complete lack of activity of the gamma-system, or to a gamma-system which is already over-excited and cannot increase its rate of discharge any further.

The technique of Magladery (op. cit.), as extended by Paillard (1955 a, 1955 b) is much more likely to be of value. This application of classical neurophysiological technique involves repetitive stimulation of the afferent fibres in the medial popliteal by two stimuli - one conditioning stimulus and one testing stimulus.



a.



b.

Fig. 16.

Fig. 16 - Normal subject.

a) The "H" wave. Time 500 c/s.

b) The effect of a contraction of the leg muscles during the Jendrassik manoeuvre. Time 500 c/s.

By varying the intensity of the stimuli and their separation, it is possible to obtain a great deal of information about the cycle of excitability changes of the anterior horn cells following stimulation, and the various influences affecting it. If mechanical stimulation of the tendon is substituted for each of the electrical stimuli in turn, and then for both, additional information will be obtained about the stretch receptors.

The study of the effect of convulsions on the tendon reflexes could also be extended by using the techniques already described after electroconvulsive therapy (E.C.T.) or other types of induced convulsions. In this way more adequately controlled experiments could be carried out. I had hoped to carry out such experiments but was unable to do so as the laboratory where this work was done was too far from any hospital where E.C.T. was in use, and the apparatus too cumbersome to transport. Future employment in a psychiatric hospital may afford opportunities for this investigation to be carried out. It may also provide opportunities for work on catatonic rigidity and drug-induced Parkinsonism.

The field is certainly open for further pharmacological studies. Dordoni (1948) has reported that Sherringtonian (i.e. 'gamma') rigidity was markedly reduced in the decerebrate dog by the injection of 0.8 mg/Kg of morphine whereas a dose of 4 mg/Kg was entirely ineffective in the 'Pollock and Davis' animal.

Apomorphine, on the other hand, was active in both cases. A similar dissociation has recently been described by Henatsch and Ingvar (1956) using chlorpromazine.

The effect of phenytoin on the reflex arc has already been described and there is some suggestion that other anticonvulsants may have similar effects. Recently Struppler and Schenck (1961) have found that barbiturates also produce a depression of tendon reflexes in man without affecting the "H" wave.

Other pharmacological experiments include the comparisons which have been carried out of the relative sensitivity of the monosynaptic and polysynaptic reflex responses to a variety of agents, including nembutal, myanesin, curare, and strychnine in the cat. These are reviewed by Brooks and Koizumi (1953). Much of this work could be repeated in man. Indeed, such repetition is essential before the claims of manufacturers of various drugs reputed to reduce spasticity and rigidity can be taken seriously.

In the realm of extrapyramidal disorders, the introduction of stereotaxic operations in man now permit the stimulation of, and recording from, restricted areas in the the thalamus and basal ganglia. It would be of great interest to know something of the behaviour of muscle spindles and the excitability of the anterior horn cells during such procedure.

These are only some of the many investigations that could be carried out in the comparatively unexplored field of spinal reflex physiology in man.

SUMMARY

The aim of this thesis has been to investigate the cause of the loss of tendon reflexes in a variety of clinical conditions where this sign has usually been left unexplained or given a totally unconvincing explanation. It is suggested that some of the difficulty arises from a failure to apply to this problem current neurophysiological ideas concerning the motor innervation of muscle spindles.

To this end, all patients with absent tendon reflexes admitted to the wards of a neurological unit were investigated. A few additional cases were obtained from other hospitals.

The series included patients with Friedreich's ataxia of 'pure' and 'mixed' forms, patients with tumours and atrophy of the cerebellum, cases of disseminated sclerosis with lesions above the level of the particular reflex involved, cases of the Holmes-Adie syndrome, of Parkinsonism and of polymyositis and patients who had absent tendon-reflexes after intrathecal injection of phenol for the relief of severe spasticity. Patients with tabes dorsalis, polyneuritis, motor neurone disease and muscular dystrophy were only included to emphasise the contrast, since the areflexia in these cases has been adequately explained.

The methods used included the application of a technique already applied by others to normal subjects. This involved the stimulation of the afferent fibres in the medial popliteal nerve in such a way as to cause a reflex contraction of the calf muscles. The mechanical displacement of the foot and the electromyographic response of the calf muscles following a blow on the tendo-Achilles was also recorded. It is argued that changes in both the mechanical and the electrically induced reflex are due to influences directly affecting the alpha-motorneurones while variations confined to the mechanically induced reflex suggest changes in the excitability of the stretch receptors. This technique was supplemented in some instances by motor nerve conduction studies.

It is suggested that:

1) In the 'pure' forms of Friedreich's ataxia, in those rare cases of disseminated sclerosis with loss of tendon reflexes and in diseases of the cerebellum, the abnormality can be accounted for by an interruption or withdrawal of facilitatory impulses to the gamma-motorneurones, leaving the afferent side of the reflex arc intact, but that in the 'mixed' forms of Friedreich's ataxia, the lesions in the peripheral nerves are sufficient to account for the areflexia.

2) Phenytoin given in moderate doses may produce this effect on supraspinal control of the gamma-motorneurones, but if given in larger doses, it may depress synaptic transmission in the spinal cord.

3) A similar disturbance of the motor innervation of muscle spindles may also occur in Parkinsonism where there may be a depression of the monosynaptic stretch reflex with a simultaneous enhancement of the polysynaptic stretch reflexes.

4) Phenol injected intrathecally blocks the gamma-efferent fibres but in those patients who show lasting sensory disturbances there is an additional effect on the afferent fibres.

5) In some cases of polymyositis with loss of tendon reflexes in the absence of marked weakness there may be a lesion in the muscle spindles themselves or in the terminal intramuscular afferent nerve fibres, although this will require histological confirmation.

6) In tabes dorsalis and polyneuropathy the lesions in the posterior nerve roots and in the peripheral nerves are sufficient to account for the areflexia.

7) In the Holmes-Adie syndrome a disturbance of synaptic transmission in the spinal cord is postulated.

8) In motor neurone disease and muscular dystrophy, the lesion is, not surprisingly, on the motor side.

Suggestions are made for further research in this field.

Appendix 1

The Relative Importance of the Gastrocnemius and Soleus Muscles in the Ankle Jerk of Man.

In many laboratory animals there is a clear structural and functional differentiation between 'red' and 'pale' muscle (Creed et al 1932). This differentiation is well exemplified by the triceps surae which comprises the red soleus and the pale gastrocnemius. It has been known for a long time that these muscles differ functionally both in the duration of their contraction and in their behaviour during reflex contraction (Denny-Brown 1929; Creed et al 1932) the soleus taking a greater part in this contraction than the gastrocnemius.

Although there is no very clear-cut structural difference between these muscles in man, Walls (1953) has shown that the total granularity (based on lipoid granule content) of the muscle fibres in the soleus was greater than those in the gastrocnemius. There has been a growing feeling backed by very little experimental evidence that some sort of functional differentiation exists (Tokizane 1955, Bergamini 1959).

Paillard (1955 a, 1955 b) has already noted casually that during his experiments on electrically induced reflex contraction of the calf muscles he preferred to place his electrodes on the soleus muscle, and a number of other workers (Denny-Brown 1949, Joseph

and Nightingale 1952, Naponiello 1957) have shown that in the standing position the activity of the soleus is much greater than that of the gastrocnemius which is said by some (Denny-Brown 1949),(Joseph and Nightingale 1952) to be often entirely inactive.

This part of the study was carried out in order to see whether during a reflex contraction of the calf muscles there was any difference in the relative participation of the soleus and gastrocnemius.

Methods:

1) The ankle jerk was produced as described earlier.

2) The skin electrodes already described were used to record the electromyographic response of the muscles. This was preferred to needle electrodes as it was considered that a better assessment of the behaviour of the whole muscle could be obtained in this way. A pair of electrodes was placed on each of the two muscles. In some of the early experiments recordings were also taken with monopolar electrodes, an indifferent electrode being placed on the external malleolus for the soleus and the head of the fibula for the gastrocnemius. Since the results obtained in this way did not differ appreciably from those obtained with bipolar recording and since it led to difficulties with stimulus artefact and 50 cycles/sec. interference, this method was abandoned.

3) A tension recording was also obtained using the transducer previously described.

4) The medial popliteal nerve was stimulated so as to produce an "H" wave and a simultaneous displacement in the tension recording.

Results:

Twelve normal subjects were used. In every case both legs were tested. Figure 17 shows the sort of result that was obtained. In every instance the electromyograph of the ankle jerk showed a consistently greater deflection when the record was taken from the soleus than when it was taken from the gastrocnemius. The jerk itself was constant throughout as is shown by the tension record.

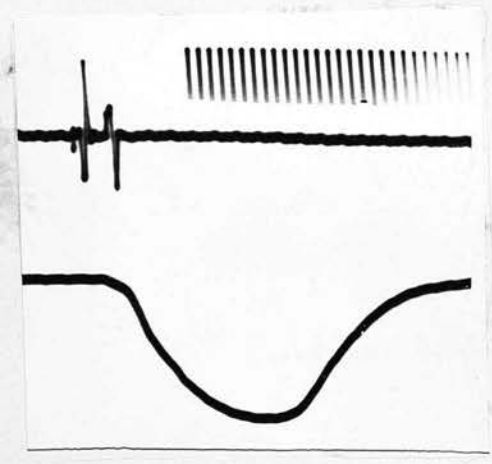
The same applied to the "H" wave. For an equal contraction it was consistently greater in the record obtained from the soleus than in that obtained from the gastrocnemius (figure 17).

The reverse applied to the "M" wave which was always larger in the gastrocnemius record than in the soleus record (figure 18).

When the stimulus was increased so as to produce a maximal "H" wave this was again larger in the soleus. The threshold for reflex contraction, however, was not appreciably different in the two muscles whether the stimulus was mechanical or electrical.

a.

b.



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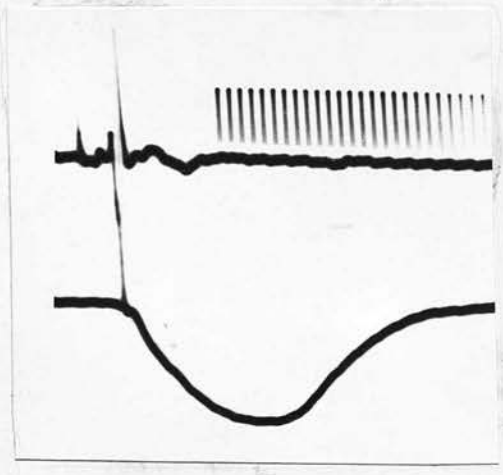


d.

Fig. 17

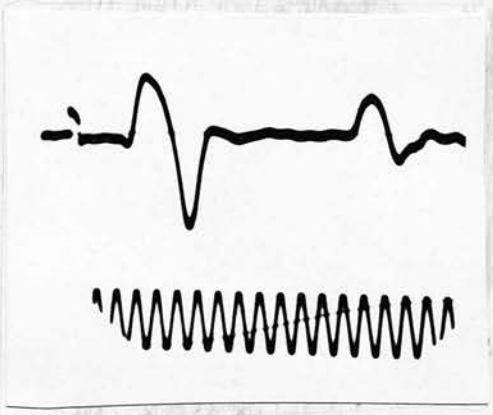
Fig. 17 - Normal subject.

a) Electromyographic response of gastrocnemius muscle (top trace) during the ankle jerk (bottom trace). Time 100 c/s.

b) The same from the soleus muscle.

c) "H" wave (top trace) from the gastrocnemius muscle and the associated displacement of the foot (bottom trace). Time 100 c/s.

d) "H" wave (top trace) from the soleus muscle and the associated displacement of the foot (bottom trace). Time 100 c/s.



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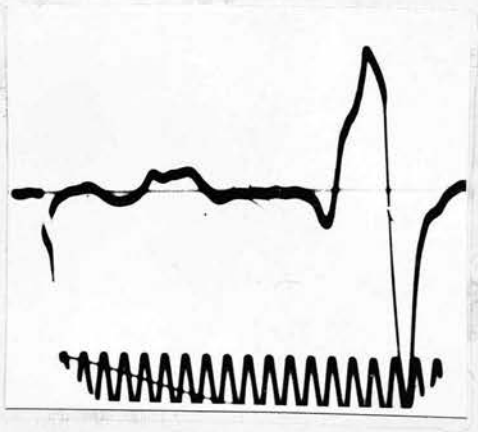

b.

Fig. 18.

Fig. 18 - Normal subject.

a) The "M" and "H" waves as recorded over the gastrocnemius muscle. Time 500 c/s.

b) The "M" and "H" waves as recorded over the soleus muscle following a stimulus of the same size as was used in a). Time 500 c/s.

Discussion:

It would therefore appear that during a reflex contraction in man, a larger action potential is recordable from the soleus than from the gastrocnemius. That this is not due to extraneous factors like any difference in the resistance of the tissues overlying the two muscles is suggested by the fact that direct stimulation of the motor fibres produced a larger action potential ("M" wave) in the gastrocnemius.

The results are therefore in keeping with those of animal experiments. Eccles et al (1958) found that in the cat motorneurones of 'red' muscles had a larger total post-synaptic potential than those of 'pale' muscles.

This may be linked to the fact that, at least in animals, the density of muscle spindles is greater in the soleus muscle (Hagbarth and Wohlfart 1952, Swett and Eldred 1960, Cooper 1960) and this muscle may be expected to be more sensitive to stretch than the gastrocnemius; and also with the differences in central connections between the two muscles (Eccles et al 1957).

Unfortunately it is impossible to tell whether the greater electrical activity of the soleus is necessarily associated with a greater contraction since such an analysis would require the dissection of the respective tendons and a direct recording of the tension developed by each muscle. This is obviously not feasible in man.

However, it would seem reasonable to assume that a greater contraction does in fact occur. The results do at any rate suggest that there is a difference in the behaviour of these two muscles during a reflex contraction and this is consistent with the greater activity of the soleus in standing (Denny-Brown 1949; Joseph and Nightingale 1952; Naponiello 1957) since normal posture must be based on the stretch reflex.

In summary then, in twelve normal subjects the composite action potential recorded by means of skin electrodes during a reflex contraction was greater over the soleus than over the gastrocnemius. It is suggested that the soleus plays a greater part in the production of the ankle jerk.

Appendix II

Case histories of patients with 'mixed' forms of Friedreich's ataxia

M.M. This 20 year old woman presented with a difficulty in walking of 12 years duration. This was of a spastic nature. She was originally seen by an orthopaedic surgeon who carried out a plaster correction of a foot deformity. More recently she had developed a weakness of both hands and had begun to get unsteady on her feet. There was no relevant family history.

On examination the cranial nerves were intact. There was no nystagmus. There was wasting and weakness of the intrinsic muscles of both hands and peripheral wasting in the lower limbs. The dorsiflexors of both feet were weak. The ankle jerks were absent and both plantar responses were extensor. Her gait was slightly ataxic but there was no abnormality of sensation.

R.McK. This 14 year old boy was first noticed to have an abnormal gait by his mother. He was 7 years old at the time and she was struck by the fact that he dragged his feet when walking. He was referred to an orthopaedic surgeon who advised postural and walking exercises. His condition improved a little and then remained static until about 2 years before admission. He then noticed that the toes of both feet turned in when he was walking and that his gait had lost its 'spring'. This tendency to invert became steadily worse and interfered with his ability to play games with other children. More recently he had become subject to frequent cramp in both calves which usually came on after a hot bath. He had three siblings all unaffected and there was no family history of any significance.

On examination he was found to have horizontal nystagmus. There was peripheral wasting in all four limbs and some wasting around the right shoulder girdle but no fasciculation. All the affected muscles were noticeably weak, especially the peronei. All tendon reflexes were absent. The abdominal reflexes were present. The left plantar response was extensor, the right equivocal. There was a loss of proprioception in both hands and feet and vibration sense was absent below the hip on the right side.

Exteroceptive sensation was normal. He had bilateral pes cavus and a mid-dorsal kyphoscoliosis convex to the right.

Investigations:

Haemoglobin 90%

Sedimentation rate 4 mm in the first hour

Urine normal

Lumbar puncture Protein 40 mg/loo mls

Colloidal gold curve - negative

No cells seen

W.R. negative

X-Ray of skull and chest normal

F.McK. This 14 year old girl first started to have difficulty in walking about 10 years before admission. This appears to have been mainly of an ataxic nature. There was a steady progression in her unsteadiness and she found it more and more difficult to take part in games with other children. Lately she had noticed a difficulty in writing.

She had two brothers, both normal and no other member of her family was affected.

On examination the cranial nerves were intact. There was no nystagmus and her speech though slow was probably normal. There was wasting and weakness and hypotonia in both upper and lower limbs and more marked peripherally. All the tendon jerks were absent but the plantar responses were extensor. Sensation was normal. All four limbs were inco-ordinate, the gait being broad-based and ataxic. She also had a moderate lumbar lordosis.

Investigations:

Haemoglobin: 105% (Sahli)

White blood count: 8,000 per cu.mm

Sedimentation rate: 32 mm in the first hour

Urine: Specific gravity 1.027

No albumin, sugar or acetone

Lumbar puncture: Pressure normal

Protein 35 mg/100 mls

Colloidal gold curve negative

No cells

W.R. negative

X-Ray of skull and chest normal

M.H. This 13 year old boy was noticed to have a foot deformity when he was aged 7. Lately his gait had become awkward and his feet tended to bang heavily down on the ground. His mother had had bilateral nerve deafness since the age of 20 but the rest of the family including his two brothers had had no illness of any relevance.

On examination there were no cranial nerve or upper limb abnormalities. He had bilateral weakness of the hip flexors, hamstrings and dorsiflexors. All tendon jerks were sluggish. The plantar responses were both extensor.

Investigations:

Haemoglobin and sedimentation rate: normal

Urine: normal

Lumbar puncture: Pressure normal

Protein 80 mg/ 100 mls

No cells

W.R. negative

M.C. This woman was 52 when she was seen. She was said to have had an abnormal gait from early childhood. Over the years she had noticed that she was becoming increasingly tired.

She had one brother who had two sons, oneof whom had a similar abnormality of gait. The rest of the family was unaffected.

She had nystagmus to both the right and the left. The upper limbs were normal apart from a suggestion of early clawing. There was bilateral pes cavus with clawing of the toes. The lateral aspects of both legs were wasted and there was marked fasciculation in the right gastrocnemius. Both peronei and calf muscles and the left tibialis anterior were weak. The tendon reflexes were brisk except for the ankle jerks which were absent. The left plantar response was extensor, the right flexor. The abdominal reflexes were present. Vibration sense was absent at both ankles, and there was hypoaesthesia and hypoalgesia over the lower half of the left leg.

Investigations:

Lumbar puncture: Pressure normal

Protein: 15 mg / 100 mls

1 cell / cu.mm

Colloidal gold curve negative

K.McL. aet. 55: This patient had deformed feet from the age of 5 and had a number of corrective operations performed on him. For 18 years his gait had been unsteady but there did not appear to have been very much progression. His speech had been slurred from early infancy but he thought that it had improved lately. He had one similarly affected sibling.

On examination he was found to have a slurring dysarthria. There was a mid-dorsal scoliosis, a suggestion of clawing of both hands and bilateral pes cavus. In the upper limbs the dorsal interossei were slightly wasted and the supinator jerks absent. In the lower limbs there was fasciculation in the calves, and all tendon reflexes were absent. Both plantar responses were equivocal. Proprioception was absent at the toes, vibration sense absent below the hips and there was doubtful impairment of exteroception peripherally.

Co-ordination was very poor in all four limbs and the gait was markedly ataxic and broadly based.

W.P. aet. 43. This patient's difficulty in walking was first recognised when he was about 10 years old. It progressed until 2 years before admission he became chair bound. During the years before admission his speech had become indistinct.

In the past he had had several operations for congenital cataract. The family history, though unconfirmed, suggested that one brother had difficulty in walking. He was found to be markedly dysarthric and to have a tremor of the tongue.

The upper limbs were hypotonic and very inco-ordinate. There was wasting and weakness especially in the hands but no fasciculation. Sensation was normal. The trunk and neck muscles were also weak.

In the lower limbs there was also hypotonia and inco-ordination. Wasting was obvious from mid-thigh downwards and all movements were weak. Vibration sense was lost at the ankles but sensation was otherwise normal. The ankle jerks were absent and both plantars were extensor. The abdominal reflexes were absent.

Investigations:

Haemoglobin: 105%

Sedimentation rate: 36 mm in the first hour

Urine: normal

X-Ray of skull and chest: normal

Lumbar puncture: Pressure normal; Protein 45 mg /100 mls
Colloidal gold curve negative; Cells 4/cu.mm
W.R. negative

Case histories of patients with Disseminated Sclerosis.

G.T. aet. 25. Two weeks before admission this patient developed a severe left sided headache associated with pain and tenderness in the left eye. Very soon after, vision in the left eye became blurred and she experienced paraesthesiae and numbness over the left side of the face and scalp, the numbness rapidly spreading to affect the whole of the left side of the body.

She gave a history of having had an attack of left sided numbness and weakness of sudden onset 10 years previously, for which she had been admitted to hospital where a diagnosis of 'encephalitis' was made.

On examination she showed a marked swelling of the left optic disc with nystagmus on looking to the left. There was hyperalgesia and dysaesthesia over the left half of the body including the face. The left ankle jerk was very sluggish and the right absent. Both plantar responses were extensor. Investigation was unrevealing. She was treated with A.C.T.H. Her condition improved and the ankle jerks returned.

M.S. aet. 16. Two weeks before admission this patient developed tingling in the left side of the face including the inside of the mouth and the left side of the tongue. This tingling started in the tongue and spread to the rest of the face over a period of a week. The tingling gradually receded only to be replaced by numbnessin the affected region. The day before admission as she was getting up in the morning she suddenly felt very nauseated. The nausea increased during the whole day until she finally had to go to bed. She then felt very dizzy especially if she kept her eyes open. On the day of admission she vomited on attempting to get out of bed. She was extremely dizzy and unsteady on her feet, tending to veer to the left when walking.

On examination she was found to have a second degree nystagmus with both vertical and horizontal components and there was a failure of adduction of the left eye. She had an 'onion-skin' type of hypoaesthesia and hypoalgesia. The left side of the face was rather flatter than the right.

The left arm tended to drift and to show an intention tremor but power was normal. The tendon jerks were depressed and the right ankle jerk was absent. The right plantar response was extensor but the abdominal reflexes were present.

M.S. (contd.)

She was treated with prednisolone in a dose of 50 mg/ day for 3 days. This was gradually decreased by 10 mg at 3 day intervals. She showed a slow improvement, the numbness tending to recede from the periphery inwards. The nystagmus improved and the tendon reflexes returned.

Investigations:

Haemoglobin and sedimentation rate normal.

Urine; normal

Lumbar puncture: Pressure normal

Protein 20 mg /100 mls

Colloidal gold curve negative

No cells

W.R. negative

L.G. aet. 36. This patient's symptons started 8 years before admission with transient diplopia, numbness in the hands and failure to recognise coins. This lasted for a few weeks and finally receded spontaneously. Four years later she began to have difficulty in walking and increasing stiffness and unsteadiness of the legs.

On examination, the cranial nerves were intact. There was no abnormality in the upper limbs other than a left sided intention tremor. In the lower limbs there was a global weakness with brisk knee jerks but absent ankle jerks. The plantar responses were both extensor and the abdominal reflexes were absent. Vibration sense was depressed at the left ankle but sensation was otherwise normal.

Investigations:

Lumbar puncture: Pressure normal
Protein 50 mg/ 100 mls
No cells
Colloidal gold curve negative
W.R. negative

X-Ray of spine: normal

Case histories of patients with Parkinson's Disease.

J.F. aet. 56. This patient developed stiffness in both legs about 6 years before admission. Six months later this spread to the left arm. Sometime later the right arm and leg began to shake.

On examination, he had a typical paucity of facial expression. His voice was monotonous and his gait shuffling. There was a tremor of the right arm and rigidity of the left arm and both legs. All the tendon jerks were depressed and both ankle jerks absent. The plantar responses were flexor.

R.S. aet. 49. This patient gave a history of increasing stiffness beginning with left leg and eventually affecting all four limbs, especially the left. Walking had become progressively more difficult due to 'shuffling' and to a tendency to lean forward from the waist and at times to break into a run. There was no tremor. Salivation was a little excessive and he had some difficulty in swallowing. Concentration and memory were not affected.

R.S. (contd.)

On examination he had a mask-like face and a shuffling gait with a tendency to lean markedly to the left. There was a moderate rigidity of all four limbs more noticeable on the left side but only a minimal tremor. The tendon jerks were depressed more so on the left side and the ankle jerks were absent. The plantar responses were flexor.

A diagnosis of paralysis agitans was made and he was referred to a neurosurgeon who performed a right stereotaxic pallido-capsular lesion. This was followed by a marked improvement of the rigidity on the left side and a return of the left ankle jerk.

A.G. aet. 45. This patient was noticed at a Pensions Tribunal to have an expressionless face and a monotonous voice. His only complaint was a tendency to sleepiness and excessive salivation.

On examination he had only slight rigidity and no tremor. He did not swing his left arm when walking. The tendon jerks were all sluggish and the ankle jerks absent. Both plantar responses were flexor.

C.J. aet. 49. The patient developed a picture of mental slowing, apathy, slowness of movement and rigidity at the age of 43 following an abdominal operation. This was progressive and he soon developed a coarse tremor of both arms. His eyes also showed a tendency to close. There was no history suggestive of encephalitis.

On examination he was found to be slow and markedly deteriorated mentally. His speech was monotonous coming in bursts. Salivation was excessive and his eyes watered profusely. Conjugate ocular movements were greatly reduced and there was an inability to converge. The globellar tap was positive and his face was expressionless.

There was a 'cog-wheel' type of rigidity,more marked on the right side and slight bilateral tremor. All tendon jerks were sluggish and the ankle jerks were absent. The plantar response was extensor on the left and flexor on the right.

A diagnosis of postencephalitic parkinsonism was made.

J.M. aet. 48. This patient had a history which extended back for 10 years and consisted of increasing stiffness and pain mainly in the left limbs. Lately there had been some excessive salivation. There was no history of encephalitis and no family history.

On examination she was apathetic and her voice was monotonous. The right pupil was fixed and failed to react to light and to accommodation. Convergence was poor. Salivation was excessive and there was a tremor of the tongue. The head was held over to the right and in the limbs there was moderate rigidity on the left and mild rigidity on the right side. The reflexes were equal but the ankle jerks were absent.

All investigations, including a Wassermann reaction, an x-ray of skull and chest, E.E.G. and analysis of blood and urine were negative.

It was felt that this was a case of Parkinsonism, probably of the post-encephalitic type.

Case histories of patients with Polymyositis.

M.J. aet. 32. This patient was admitted on August 12, 1959. Since 1958 she had been troubled by stiffness in the back, a painful left leg and periodic swelling of the ankles. In February, 1959, she began to have difficulty in walking, and her left leg dragged after her. This difficulty was most marked when she was going up a stair. About two months before admission she experienced a marked worsening of all her symptons and developed a stiffness and tightness in the hands.

On examination at that time she showed weakness of flexion and extension of the left ankle and weakness of flexion of the left hip. Both ankle jerks and the left knee jerk were absent. There was also a moderate degree of ankle oedema. Her thyroid showed uniform and soft enlargement and a faint bruit was audible over it.

Investigations:

Haemoglobin: 80% E.S.R: 20 mm/hr

Blood film: negative Urine: no protein, sugar or acetone

Lumbar puncture: pressure normal with normal constituents

Serum electrolytes and plasma cholesterol normal

Liver function tests normal

Plasma proteins and electrophoretic patterns normal

P.B.I.: 6.8 % B.M.R.: plus 34%

M.J. (contd.)

Precipitin and tanned red blood cells: negative

Radio-iodine showed an active gland

Tensilon test: negative

Her condition fluctuated considerably but on the whole there was a tendency to worsening of her symptons and she developed a weakness of the flexora of the neck and the shoulder girdle muscles.

She was treated with prednisolone and thyroxine (suppressive therapy) and showed some improvement in her neurological state and a shrinking of the thyroid.

C.T. aet. 28. This patient suffered from a paroxysmal illness, starting five years previous to seeing her, and precipitated by a 'cold'. This was associated with progressive weakness and wasting of muscles. She was admitted in 1955 with severe involvement of the respiratory muscles. She required positive pressure respiration at that time. Following steriod therapy she improved and had become fully ambulant when I saw her. On examination the cranial nerves were intact.

There was considerable weakness and wasting of muscles in both upper and lower limbs, more marked proximally. This was not associated with fasciculation. All the tendon reflexes were absent. The plantar responses were flexor. There was no sensory loss.

C.T. (contd.)

Investigations:

Haemoglobin: 86% E.S.R.: 58

W.B.C.: 26,200 mainly polymophs

Tensilon test: normal

The E.M.G. results are given in the main text.

Case histories of patients with cerebellar lesions.

C.F. This 13 year old girl was admitted on April 5, 1959. Four months prior to admission she developed attacks of vomiting occurring approximately once a week. They would last for 1 - 2 hours after which she would feel relatively well. They were always associated with severe bifrontal headache. Over the same period she had become liable to 'dizzy turns'. Originally, these were associated with active exercise such as gymnastics and would come on about once a week. Later they would arise spontaneously and occur daily. They consisted of a sensation of rotation of her environment. For two weeks before admission she was noticed to have an unsteady gait, walking on a broad base. When questioned she said that she had seen double on one or two occasions. Members of her family said that recently she had been more truculent than usual.

C.F. (contd.) On examination she was found to be a pale, obese girl. There was marked bilateral papilloedema and a horizontal nystagmus especially obvious when she looked to the left. Her gait was ataxic. She walked on a broad base, tending to stagger to the left. There was a hypotonicity on the left side and the tendon jerks on that side were 'sluggish', the ankle jerks being absent. The abdominal reflexes were present and the plantar responses were flexor. There were no abnormalities of sensation.

Myodil ventriculography was performed and it showed a large space occupying lesion in the left cerebellar hemisphere.

At operation on April 8, 1959, a 25 c.c. cyst in the left cerebellar hemisphere was opened and a total removal of the tumour which formed its medial wall was effected. Histology showed this to be an astrocytoma. She was discharged on May 20, 1959, still slightly ataxic and with her papilloedema subsiding. I saw her about two years later when she showed slight left sided inco-ordination. The hypotonia and depression of tendon reflexes on the left was still obvious and the left ankle jerk was absent.

V.W. This 7 year old girl was admitted on September 10, 1957, with an eight month history of early morning vomiting and a more recent history of inco-ordination. Her parents had noticed an enlargement of her head during the preceding months.

On examination she showed bilateral papilloedema, a left 6th nerve paresis, and left-sided inco-ordination. There was hypotonicity on the left side and all tendon jerks were difficult to elicit. The left ankle jerk was absent. The right plantar response was extensor. The abdominal reflexes were present and equal. There was no abnormality of sensation.

At operation a subtotal removal of a large left-sided tumour was performed and this was followed up by a full course of deep X-Ray therapy to the posterior fossa. Histology revealed the tumour to be an astrocytoma.

She was discharged on December 11, 1957, with only mild left-sided inco-ordination and hypotonia. The left ankle jerk was still absent. When I saw her in May 1961 she still had a left-sided hypotonia and hyporeflexia and an absent left ankle jerk.

R.M.D. This 18 year old man was admitted on October 10, 1959. He had been suffering from severe frontal headaches and vomiting for 6 weeks before admission. More recently he had experienced intermittent double vision and left sided inco-ordination.

On examination he showed papilloedema, nystagmus on looking to the right, an early 6th nerve paresis, and a pupil which was slightly larger than the left. There was hypotonia and inco-ordination of the right arm and leg, and the tendon jerks were absent on the right side. The plantar responses were flexor and the abdominal reflexes present. Sensation was normal. A myodil ventriculogram showed the features of a space occupying lesion in the right side of the posterior fossa.

Operation on October 13, 1959, disclosed a cyst in the right cerebellar hemisphere with an associated tumour nodule. A biopsy showed the features of a haemangioblastoma. The cyst was evacuated and the patient later treated by radiotherapy. He was discharged on January 14, 1960, considerably improved. I saw him in April, 1961, by which time there was no papilloedema. Co-ordination was almost normal but the right ankle jerk was still absent.

J.T. aet. 56. This patient's history dates back to 1952 when he had severe difficulty with balance and gait associated with some pain in the thighs. He was at first diagnosed as having alchoholic polyneuritis but it was later changed to one of corticocerebellar atrophy of late onset. The unsteadiness gradually progressed over the years until he had great difficulty in walking unaided. More recently his writing had become affected.

On examination his speech was normal and there was no nystagmus. The cranial nerves were intact. There was an intention tremor of the hands and a very marked inco-ordination of the lower limbs. His gait was broadly based and ataxic. The lower limbs were also markedly hypotonic although there was no weakness. All the tendon reflexes were sluggish and the ankle jerks were absent. The plantar responses were flexor and the abdominal reflexes present. There was no disturbance of sensation.

Investigations were unrevealing.

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